

# *The American Journal of* DIGESTIVE DISEASES

An Independent Publication

DEVOTED TO GASTRO-ENTEROLOGY AND NUTRITION

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Volume 17

June, 1950

Number 6



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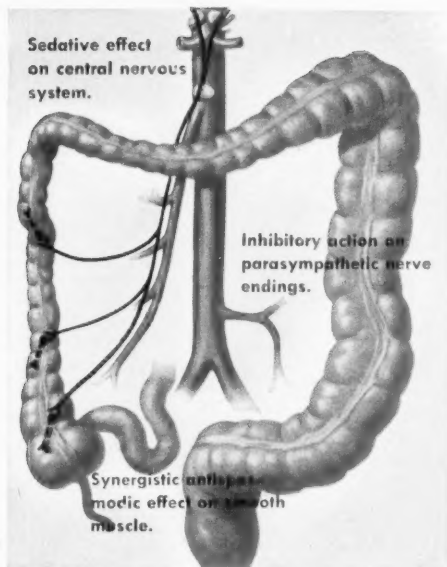
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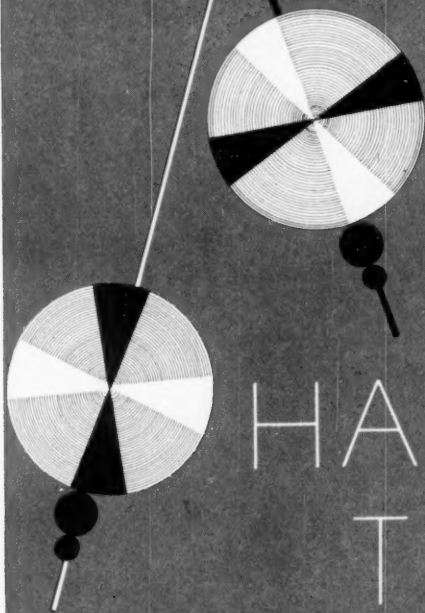
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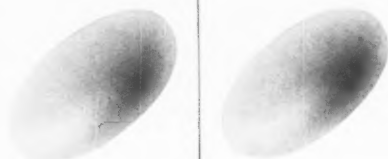
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### REFERENCES

1. Longino, F. H.; Grimson, K. S.; Chittum, J. R., and Metcalf, B. H.: An Orally Effective Quaternary Amine, Banthine, Capable of Reducing Gastric Motility and Secretions, *Gastroenterology* 14:301 (Feb.) 1950.
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## BALANTIDIASIS

J. C. SWARTZWELDER\* New Orleans, La.

**H**UMAN infection with *Balantidium coli*, the intestinal ciliate of man, although a rare disease, has been observed on numerous occasions in the South. A brief account of the clinical, pathologic, epidemiologic, and diagnostic features of this parasitic infection, with particular reference to cases which have occurred at the Charity Hospital of Louisiana at New Orleans, is included to familiarize physicians with the nature of this protozoan disease. Salient data on these cases, which represent about one-fourth of all balantidial infections recorded in the United States, are integrated with the discussion of the disease and are summarized in Table I.

Sixteen cases of balantidiasis have been recorded at Charity Hospital since 1909. Fourteen of these have occurred since 1936 and five cases of balantidial infection were diagnosed at the hospital in 1947. No reason for the unusual number of cases in 1947 is obvious. Since only 61 cases of balantidiasis in man have been reported in the United States, including those from this state, according to the literature available to me, the 16 cases which have occurred in Louisiana represent 26.2 percent of the total for the country. According to Young, (1) prior to his report in 1939, thirty-two cases of balantidial infection had been reported from 16 states. The report of Young added nine new cases from South Carolina and two cases found by Meleney in Tennessee. Additional cases which have been reported since 1939 include those of Hummel (2) De Lanney and Beahm (3) and Tsuchiya and Kenamore (4). One of the 16 cases from Louisiana was reported by Bel and Couret (5) in 1909. The remaining 15 represent more recent infections which have occurred in Louisiana. These new cases constitute the basis for this report.

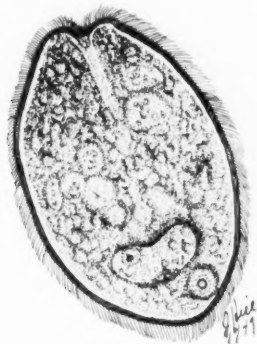


Fig. 1. Drawing of *Balantidium coli* trophozoite, showing cilia and kidney-shaped macronucleus.

\*From the Department of Microbiology of Louisiana State University School of Medicine and the Charity Hospital of Louisiana at New Orleans.

Submitted Aug. 30, 1949.

### ETIOLOGY

*Balantidium coli* is the only pathogenic ciliate of importance which parasitizes man. It is also one of the largest of the intestinal protozoa occurring in humans. Both trophozoite and cystic stages of the ciliate are recognized. In human infections, the trophozoite is far more commonly observed than is the cyst. The size of trophozoites varies considerably, ranging from 50 to 146 micra (averaging about 90 micra) in length, and 37 to 100 micra (averaging about 57 micra) in breadth. It is variously described as pear, egg- or boat-shaped. The trophozoite is somewhat narrowed at the anterior end and broader and rounded at the posterior end. In unstained preparations of fresh liquid or semiformal stools, the live trophozoites appear as large, oval, hyaline or slightly bluish-green bodies rapidly moving or gliding through the microscopic field. The organisms are easily visible with ordinary low power magnification of the microscope. The trophozoite is clothed with short delicate cilia which are constantly motile and serve to propel the parasite. This species of ciliate is

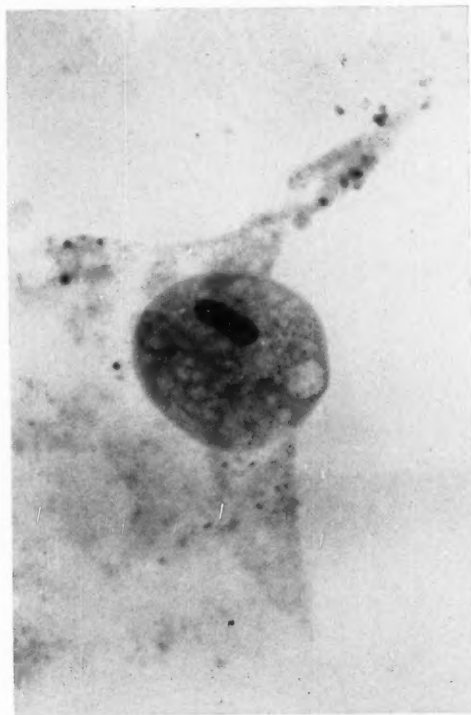


Fig. 2. *Balantidium coli* trophozoite in iron-hematoxylin stained preparation. Cilia are not apparent in this stained specimen. Note prominent nucleus.



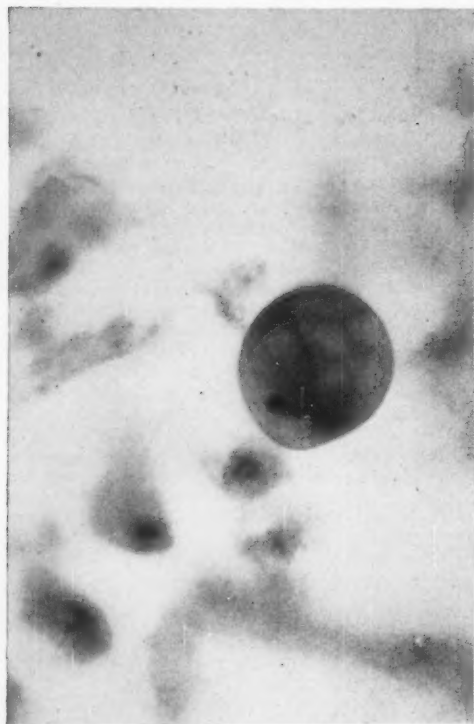


Fig 3. Cyst of *Balantidium coli* in iron-hematoxylin stained preparation.

also characterized by the presence of a large, prominent kidney-, crescentic- or sausage-shaped macronucleus which may be observed in unstained, iodine-stained or iron-hematoxylin-stained fecal smears. This structure should be demonstrated in order to identify this species and to differentiate it from free-living ciliates which may be contaminants of fecal specimens and containers. Close by, or in the concavity of the macronucleus, is a micronucleus which, due to its small size, may not be detected. Sometimes, particularly when the trophozoite is iodine-stained, the internal structure of the parasite may be obscured by the stained cytoplasmic inclusions. In addition to the cilia and prominent macronucleus, a funnel-shaped depression at the anterior end known as the peristome, anterior and posterior contractile vacuoles, and ingested food particles may be observed. The infection presumably is transmitted chiefly by the encysted form of the protozoan. The cysts are spherical or ovoid and measure about 50 to 60 micra in diameter. The cyst wall appears double and is transparent. It encloses the ciliate which occasionally may be observed rotating slowly within the cyst. Cysts might easily be mistaken for plant cells or other fecal remnants. The cystic stage appears to have been observed in less than ten percent of the human cases and in this series was detected in only one of the 16 cases.

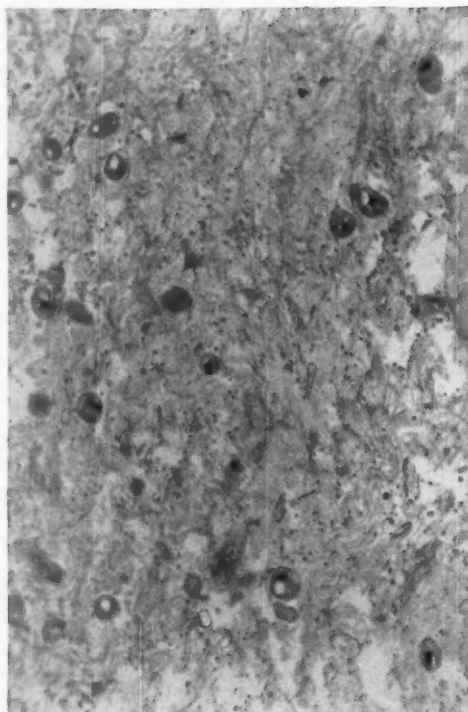


Fig 4. Section of large intestine showing numerous trophozoites of *Balantidium coli*.

#### PATHOGENICITY

Balantidiasis may resemble intestinal amebiasis to a considerable extent, both in clinical manifestations and in pathology. Asymptomatic cases occur. It has been stated that about one out of five cases detected are symptomatic. However, most of the cases diagnosed at Charity Hospital have had clinical infections. Chronic cases occurred with relative frequency in this series. These are usually characterized by recurrent attacks of diarrhea of varying severity with brief periods of intermittent quiescence. The third clinical type of the disease is dysenteric. The severity of the dysentery varies from mild to fulminating. Fatalities have resulted from balantidiasis. Strong (6) in 1904 presented an analysis of 117 cases of the disease reported in the world literature since 1857. There were 35 deaths in the above series, representing a mortality of 30 percent. However, in a few of the cases death resulted from other causes. One fatality from balantidiasis occurred at Charity Hospital and was reported by Bel and Couret (5).

Diarrhea was the chief complaint of 11 cases in this series. Two additional patients, on questioning, stated that diarrhea was occurring. In these 13 cases the number of bowel movements per day ranged from about 5 to 25. Eight of 10 individuals queried, gave a history of dysentery either prior to or at the time of admission.

Two denied the presence of gross blood. Loss of weight was extreme in a few cases and slight in some others. Occasionally there was abdominal pain and less commonly abdominal tenderness. The duration of the present illness prior to admission ranged from one week to two years. It exceeded one month in 9 of 13 cases. In other cases reported in the literature, chronic infections have apparently persisted well over a decade. A characteristic offensive odor noted in some patients was described by an attending physician as resembling that of a pigpen. A peculiar fetid odor of the breath has been noted by other workers (3). Amebiasis, nutritional deficiency and shigellosis were suggested most frequently as tentative diagnoses in this series of cases. Many of these cases had complicating infections with intestinal nematodes, chiefly *Ascaris lumbricoides* and *Trichocephalus trichiurus* (whipworm).

According to Strong (6) gross lesions were observed in the large intestine in 28 of 31 necropsies of cases of balantidiasis. In the remaining 3 cases, no gross ulceration of the large bowel was detected. In two of the 31 cases there was generalized peritonitis. The intestinal mucosa was not normal in appearance in any of the cases in which *Balantidium coli* was found (6). The lesions of *Balantidium coli* infection in man are similar in appearance and distribution to those of intestinal amebiasis. They are usually confined to the large intestine, especially in the cecum and sigmoid colon. They

are discrete. The intervening mucosa may be either normal in appearance or somewhat hyperemic. The orifices of the ulcers vary from pinpoint to large size. Petechiae may be seen in the mucosa. The lesions may be shallow or deep and can involve mucosal, submucosal and muscular layers. Typical amebic-like undermined ulcers with overhanging edges occur.

Sigmoidoscopic examination was done in 9 cases in the present series. Lesions were observed in 7 cases, including once at necropsy. As viewed through the sigmoidoscope, the lesions often appear as shallow, punched-out ulcers with a round or irregular orifice. They are occasionally coated with a white membrane. A yellow fluid may exude. Petechial lesions which bleed easily may be present. The mucosa frequently is inflamed. De Lanney and Beahm (3) described irregularly-shaped diphtheritic patches in the mucosa varying from 1.5 to 3 cm. in length and 0.5 to 1.5 cm. in width. They also observed numerous small, round, white plaques with the appearance of bacterial cultural colonies. When the plaques were wiped off, a raw hyperemic area from which blood exuded was exposed.

#### EPIDEMIOLOGY

The pig is an important animal reservoir of balantidial infection. High incidence of infection of swine with a species of *Balantidium*, apparently identical morphologically with the form occurring in man, has

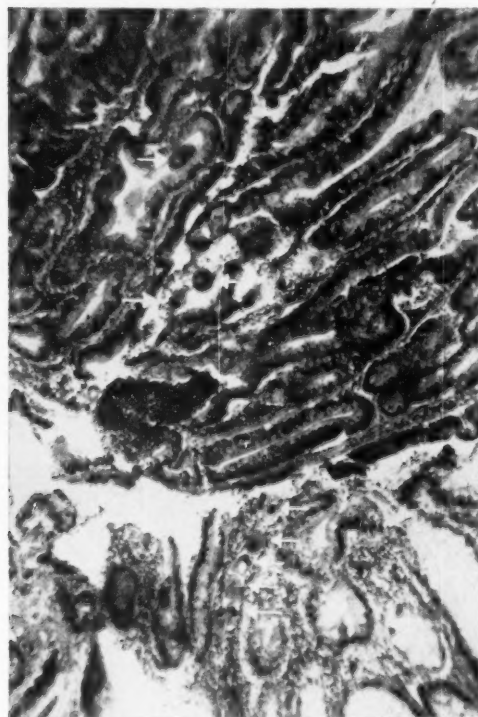


Fig. 5. Trophozoites of *Balantidium coli* in mucosa of large bowel.



Fig. 6. Section of mucosa of large intestine showing trophozoites of *Balantidium coli*.

been reported. Man is only an occasional host of the parasite. About 25 percent of reported human infections give a history of contact with pigs. Handling and slaughtering hogs and use of hog excrement for fertilizer are possible means of exposure to balantidial infection. Encystment of the parasite appears to be more frequent in the pig than in humans. Although the cystic form of *Balantidium coli* is presumably the primary infective agent involved in transmission, some evidence derived from experimental infections with *Balantidium* in guinea pigs indicates that trophozoites may also be infective by mouth under certain conditions.

Species of *Balantidium* occur in man, lower primates,

pigs, rats and guinea pigs. The *Balantidium coli* of man can be transmitted to the pig, monkey, guinea pig, cat and rat. The *Balantidium* of the hog can be transmitted to the monkey, guinea pig, rat and rabbit. The form found in the monkey is transmissible to the hog. Limited attempts to infect man with the *Balantidium* of hogs and monkeys have been unsuccessful thus far. It is probable that man is very resistant to infection with the parasite. Despite failure of a few attempts to infect man experimentally with the *Balantidium* of hogs, epidemiological evidence points strongly to the hog as the source of human infection with balantidiasis. The infection may be contracted from human

TABLE I

Case No.	Year	Sex	Age	Color	Occupation	Residence-Parish. (Rural R)	History of Contact with Hogs	Complicating Infections	Chief Complaints	Diarrhea (motions/day)	Dysentery
1.	1909(5)	M	40	C	Railroad laborer & farmer	Apparently rural	Raised hogs	None	Diarrhea Abdominal pain	— (20-24)	+
2.	1915	M	45	W	Farmer	R	—	Hookworm Whipworm	Abdominal pain	+	No
3.	1936	M	65	W	Farmer	Pointe Coupee R	—	None	Diarrhea	— (10-12)	+
4.	1937	M	15	W	Farmer	St. Landry R	—	Ascariasis Whipworm Malaria Possible pneumonia	Abdominal pain. Fever	—	—
5.	1937	M	10	W	School	Lafourche R	—	Ascariasis Whipworm Appendicitis	Pain in RLQ	— (4-6)	—
6.	1941	M	61	W	Farmer	E. Carroll	Raised hogs	None	Diarrhea	— (25)	+
7.	1942	F	2	W	—	Ascension R	—	Ascariasis Whipworm	Diarrhea Vomiting	+	+
8.	1946	M	2	W	—	Jefferson R	Family raised hogs	Ascariasis Whipworm Pinworm	Diarrhea	— (5-6)	—
9.	1947	M	15	C	None	Orleans (institution)	—	Hookworm Whipworm	Diarrhea	— (10-15)	+
10.	1947	M	58	C	Farmer	Iberville R	—	Dientamoeba fragilis	Diarrhea	— (4-6)	+
11.	1947	M	7	C	School	St. Charles R	—	Ascariasis Whipworm	Diarrhea	+	—
12.	1947	F	37	C	Housewife	St. Landry R	—	Ascariasis Whipworm	Headache, fever, vomiting, diarrhea	— (3-4)	No
13.	1947	F	4	C	—	Assumption R	—	Whipworm	Diarrhea	— (4-5)	+
14.	1948	M	11	C	School	St. Mary & Jefferson	—	Whipworm Giardiasis	Complaints not related to balantidiasis	—	—
15.	1949	F	32	C	Housewife	St. Landry R	—	Syphilis Whipworm	Diarrhea dysentery, abdominal cramps and pain, tenesmus backache, malaise, weakness	— (4-5)	+
16.	1949	F	4	C	(Daughter of farmer)	Assumption R	—	Diphtheria Ascariasis Whipworm	Not related to balantidiasis	No	No

+ = present  
— = No information

sources under insanitary institutional conditions (1).

Three of the individuals of this series questioned on the subject stated that they or their families raised hogs on the premises. Most of the adult males in the series were farmers. All except one of the 16 cases were residents of rural areas. The exception was an inmate of a New Orleans institution. In view of the rural residence and occupation of farming of many of the individuals, there is likelihood that several others were exposed to infection through contact with hogs.

Fifteen of the 16 individuals lived in a parish located in the southeastern part of Louisiana. This geographic distribution is probably influenced by the source, from

this area of the state, of a major portion of the hospital admissions.

The disease is not restricted to any particular age group. The cases in this series ranged from 2 to 65 years of age. Two patients were children of two years. Six individuals were 10 years or less. Six of the 10 other patients were 37 or more years of age. Physicians engaged in pediatrics, internal medicine or general practice should be aware of the occurrence of this infection in both the young and old alike. The infection occurred more frequently in males than in females, in the ratio of 11 to 5. The series included 7 white and 9 colored individuals.

TABLE I (Continued)

Weight Loss	Duration Prior to Admission	Fatal	Tentative Diagnoses	Diagnostic Procedures	B. coli Trophozoites Observed	B. coli Cysts Observed	Lesions Observed
+	1 year	Yes	Resembled amebiasis	Stool exam.	+	No	— (1)
(70 lbs.)							(necropsy)
+	1 mo.	No	—	Stool exam.	+	No	— (2)
(emaciated)				Sigmoidoscopy			
+	5 mo.	No	Intestinal parasites	Stool exam.	+	No	— (3)
(slight)				Sigmoidoscopy			
—	1 wk.	No	Malaria	Stool exam.	+	No	— (4)
(under-weight)			Intestinal parasites	Sigmoidoscopy			
—	2 days	No	Appendicitis	Found in section of appendix	+	No (in appendix)	— (5)
+	7 mo.	No	Amebiasis	Stool exam.	+	No	— (6)
(52 lbs.)			Shigellosis	Sigmoidoscopy			+
—	1 wk.	No	Intestinal parasites	Stool exam.	+	No	— (7)
(under-weight)			Drug poisoning				
—	About 2 yrs.	No	—	Stool exam.	+	No	— (8)
+	6 mo.	No	Nutritional deficiency	Stool exam.	+	No	— (9)
+	8 mo.	No	—	Sigmoidoscopy			+
(slight)		No	Possible nutritional deficiency	Stool exam.	+	No	— (10)
—	—	No	—	Sigmoidoscopy			— (11)
—	1 wk.	No	FTO (possible typhoid)	Stool exam.	+	No	— (12)
—	8 mo.	No	Amebiasis	Stool exam.	+	No	— (13)
—	—	No	Shigellosis	Sigmoidoscopy			+
—	—	No	—	Stool exam.	+	No	— (14)
+	7 mo.	No	Amebiasis	Stool exam.	+	No	— (15)
—	—	No	—	Sigmoidoscopy			+
—	—	No	—	Stool exam.	+	No	— (16)

## DIAGNOSIS

The specific diagnosis of balantidiasis is based upon demonstration of trophozoites or cysts of *Balantidium coli* by examination of stools or of sigmoidoscopic aspirate. As noted previously, cysts were found in only one case in this series, whereas trophozoites were observed in all cases. Direct smears of one or more stool specimens sufficed for the demonstration of trophozoites of *Balantidium coli* in 15 of these cases. In the remaining patient, the ciliate was detected in a surgical specimen, i. e., section of appendix. Usually the parasites were numerous when observed in direct smears. However, negative stool specimens were occasionally interspersed with positive stools obtained on different days prior to treatment. Spontaneous temporary disappearance of the parasite from the stool makes requisite the examination of several stool specimens and of sigmoidoscopic aspirate as criteria for diagnosis or exclusion of this parasitic infection. In some stools the ciliates rapidly lose their motility and disintegrate within a few hours. Examination of the stool promptly after passage is necessary for most efficient diagnosis. The large size, typical motility, presence of cilia and the characteristic kidney-shaped appearance of the macronucleus render specific diagnosis easy. Although the zinc sulphate centrifugal flotation technic is not satisfactory for levitating trophozoites, its use routinely in stool examination as a supplement to the direct smear technic is advisable and may detect cysts of the parasite which otherwise might be overlooked. Sigmoidoscopic examination was done on 9 cases. This procedure proved a valuable supplement to stool examination as a diagnostic measure, to view lesions and to obtain material for microscopic examination. It was also of value in observing the effect of therapy. Lesions were observed with this procedure in at least six cases.

## TREATMENT

Evaluation of therapy of balantidiasis should rest upon results of repeated stool examinations over a period of at least several months, supplemented by sigmoidoscopy. Since post-treatment examination in most of the cases in this series did not meet the above requisites, and, as a number of drugs were employed in only one or two cases each, a valid estimate of the efficacy of the compounds is not possible. However, none of the drugs employed to treat these cases, including carbarsone, diodoquin, chiniofon and atabrine, was completely effective in eradicating the balantidial infection. Some clinical response was obtained from the first three compounds. One case failed to be cured by successive courses of medication with diodoquin, carbarsone and chiniofon. Hexylresorcinol, employed to treat helminthiasis in some of these patients, failed to have any significant therapeutic effect on the ciliate infection. Stool and sigmoidoscopic examinations were negative for *Balantidium coli* and for lesions immediately following treatment with Stovarsol in the one case in which this drug was employed, but there was no opportunity for further examination. Young and Burrows (7) reported successful treatment of 7 cases of balantidiasis with carbarsone. In two cases, a second course of treatment was necessary to eradicate infection. (7) De Lamey and Beahm (3) reported cure with diodoquin of a case of the disease which failed to

respond to carbarsone. Emetine is considered to be of little therapeutic value for balantidiasis. It appears that drugs reportedly effective in the treatment of some cases fail to achieve the same result in other cases. Since carbarsone and diodoquin afford clinical amelioration of balantidiasis and appear in some reported cases to eradicate the infection, for lack of more consistently effective therapeutics, it seems advisable at present to use these drugs individually or as supplements to each other. Repeated courses of treatment may be necessary. It is possible that other arsenical and iodoxyquinoline amebicides which have not had adequate trial and evaluation may be of value in the therapy of balantidiasis.

## SUMMARY

An analysis of 16 cases of balantidiasis diagnosed at the Charity Hospital of Louisiana at New Orleans has been presented. The series includes 15 new cases and represents more than one-fourth of all the available reports of the disease in the United States. Five cases were diagnosed in 1947. The series included 11 males and 5 females. The age range was 2 to 65 years. Six individuals were 10 years or less and 6 of the 10 other patients were 37 or more years of age. Thus, recognition of the disease is of importance to both pediatricians and internists. Six of 7 adult males were farmers. All except one of the 16 patients were residents of rural areas. Three of the individuals questioned on the subject stated that they or their families raised hogs on the premises. In view of the occupation of farming and of the rural residence of many individuals, there is likelihood that several others were exposed to infection through contact with hogs. One fatality, previously reported, occurred in the series. Diarrhea, dysentery, abdominal pain and loss of weight were common complaints. The duration of illness ranged from one week to 2 years. It exceeded one month in 9 of 13 cases. Amebiasis, nutritional deficiency and shigellosis were suggested most frequently as tentative diagnoses. *Balantidium coli* trophozoites were observed in all cases, whereas cysts of this parasite were detected in only one of the 16 cases. Since the parasites may temporarily fail to appear in the stool, without treatment, criteria for diagnosis should be based upon examination of several stool specimens and upon sigmoidoscopy. Sigmoidoscopic examination proved a valuable supplement to stool examination, both as a diagnostic measure, to view lesions and to obtain material for microscopic examination, and as a means of observing the effect of therapy. Limited data on treatment of the cases in this series did not permit precise and valid evaluation of the drugs employed. Although temporary clinical amelioration was afforded by certain amebicidal drugs, completely effective results were not obtained. Drugs which were apparently effective therapeutics in some reported cases have failed to achieve the same result in others. Based upon the experience of Young and Burrows (7), carbarsone appears to give the most consistent therapeutic results. When infections do not respond to a single course of carbarsone, a repeated course of therapy with this drug and/or supplementary treatment with diodoquin appears to be the advisable course.

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## FACTORS IN THE RATE OF DEVELOPMENT OF VASCULAR LESIONS IN THE KIDNEYS, RETINAE AND PERIPHERAL VESSELS OF THE YOUTHFUL DIABETIC

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## INTRODUCTION

THE use of insulin has enabled diabetic children and diabetic youths to live long enough so that the causes and the incidence of vascular lesions in youth can now be studied. Attention was early focused upon the duration of diabetes as a chief factor influencing the frequency and extent of vascular lesions, but recent observations emphasize the importance of the character of treatment and the degree of diabetic control thereby attained in the prevention of premature vascular degeneration. As early as 1929 in studying coronary arteriosclerosis Graybiel and Root (1) found that angina pectoris and coronary occlusion were three times more frequent in patients who had had diabetes for ten years or more than it was in patients with diabetes of shorter duration. Joslin (2) has emphasized the increasing frequency of deaths from arteriosclerosis as the duration of life of diabetic patients increased and, indeed, as the insulin era lengthened. Recently Dolger (3) stressed the great frequency of retinal hemorrhages. White and Waskow (4) leave a more optimistic view with regard to childhood diabetes. Nevertheless after fifteen years of diabetes the frequency of vascular lesions in kidneys, heart and retina has been high and nephritis has taken first place as a cause of death in such diabetic children after twenty years of diabetes.

Further study of patients developing diabetes between the ages of fifteen and thirty years with particular reference to the relation between the character of diabetic control attained and the rate of development of vascular lesions is desirable.

*Standards of Control.* Although the long duration of diabetes has long been considered an important factor in the development of vascular disease and nephritis, the influence of the type of treatment and the degree of control maintained now appears equally or even more decisive. A description of our standards of control follows.

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## POOR CONTROL

Patients with coma one or more times, constantly elevated blood sugar values whenever the patient has received an office examination and glycosuria constantly present represent poor control. No measurement of diet was employed and the patient made only rare tests of the urine at long intervals. The use of insulin was usually not begun until some years after the onset of diabetes. Follow-up records indicate that the patient is rarely but occasionally sugar free and laboratory tests usually are bad at the office. Such patients are not measuring a diet in any quantitative fashion although they cannot be said to be on an entirely free and unlimited diet.

## FAIR CONTROL

Patients who have never had coma after receiving initial instructions. Urinary tests are made regularly. The patient has made a faithful effort to follow his diet and instructions. Tests for urine and blood have been made at frequent intervals by a physician and are occasionally normal. Use of insulin was begun at or soon after the onset of diabetes, and frequent adjustments of diet and insulin have been made. Certain patients (not included in this series) have been awarded the Victory Medal after having had diabetes for 25 years. In twenty such patients, x-ray examinations of arteries show no calcification, blood pressure and heart are normal, urine contains no albumin and retinae are free from hemorrhages or exudates. They began the use of insulin within 2 years after onset and have consistently endeavored to control the condition by regular urine tests and frequent adjustments of diet and insulin.

The number of diabetic patients in the United States whose diabetes began during the age period of fifteen to thirty years is unknown. However, recently Root (5) arrived at a conservative estimate of at least 60,000 living cases of diabetes between the ages of fifteen and thirty. If to this figure is added those individuals whose diabetes began earlier and those now between fifteen and thirty years of age who will soon develop diabetes, an even larger estimate would be required.

In the Joslin series of 30,000 diabetic patients, 3500 developed diabetes between the ages of fifteen and thirty



years. Of this group, 310 have died. It must be remembered, therefore, that in this report unselected patients have been studied who have survived diabetes for a material period.

TABLE I

VASCULAR DISEASE IN 282 PATIENTS WITH ONSET OF DIABETES BETWEEN 15 AND 30 YEARS OF AGE

Duration years	Cases number	Females—164
0-9	90	Males—118
10-19	131	
20-29	61	
Total	282 cases	

	Cases	Per Cent
Retinitis	107	38
Retinitis Proliferans	7	3
Hypertension	70	25
Nephritis	51	18
Calcified Arteries	135 out of 234 cases	58
Vascular Disease	200 out of 282 cases	71

*Clinical Material.* In Table I are summarized 282 patients whose diabetes began between the ages of fifteen and thirty years. The usual predominance of females is illustrated by the fact that 164 of these patients were females and 118 were males. One hundred and eleven of the females are married and in a total of 143 pregnancies, 40 per cent ended in abortion, miscarriage or stillbirth. This in itself is a striking fact if it is compared with the statements by Priscilla White to the effect that among 202 diabetic women seen between 1898 and 1936 out of 309 pregnancies only 53 per cent in the preinsulin and 60 per cent in the insulin era resulted in living births. The incidence of vascular complications in our patients was high, since 200 of the patients studied manifested some form of vascular disease, an incidence of 71 per cent. This figure includes all types of vascular disease, whether it be an increased capillary fragility only or retinitis, hypertension, nephritis and calcified arteries. The most common complication found was that of calcified arteries by x-ray; 135 cases out of the 234 studied for this complication showed some evidence of calcification, an incidence of 58 per cent. (See table 2).

In Table 2 are found data summarizing the records of 282 cases charted according to the duration of diabetes. It is seen that 90 patients had diabetes less than

ten years, 131 between ten and nineteen years and 61 between twenty and twenty-nine years. The average ages for the three groups increase from 27 years to 38 and finally to 49. An elevation of blood pressure indicated by a systolic pressure above 150 and a diastolic of 90 mm or above of mercury occurred in only 2 per cent of the group of short duration, but this figure steadily rose until in the 63 cases with diabetes for more than twenty years 38 per cent had hypertension. A striking parallel is seen between the elevated capillary fragility test and diabetic retinitis. The capillary fragility was measured in many patients by both the Goltzlin method and by the use of a cuff placed at the diastolic pressure for 4 minutes and counting of the petechiae in a circle measuring 6 cm. in diameter.

Elevated capillary fragility occurred in only 10 per cent of the first group and increased as the duration of diabetes went on until 67 per cent of the patients with duration exceeding 20 years showed an increased capillary fragility. Many of these patients showed in the measured area so many petechiae that counts over 300 to 400 had to be recorded even though the counts were made with great difficulty. Diabetic retinitis indicated by the deep, round hemorrhages and some areas of waxy exudates were found in 4 per cent of the cases of short duration, but in 60 percent of the patients with long duration. Retinitis proliferans, the most serious ocular complication of diabetes, was not found in patients with less than ten years' duration and occurred in 6.3 per cent of the patients with from twenty to twenty-nine years' duration. Coma has occurred in from 20 to 29 per cent of each of the three duration groups. Nephritis increased in frequency with the duration of the diabetes. The frequency of nephritis did not increase in the group with duration of diabetes ten to twenty-nine years as compared with the group whose duration was ten to nineteen years.

The most striking change associated with long duration of diabetes was the increase in the percentage of patients who showed x-ray evidence of calcification in the arteries. Thus, in the group of seventy-one cases less than ten years in duration, only 21 per cent gave this finding, but in the group of fifty-six cases with duration of more than twenty years, 88 percent showed calcified arteries in the vessels of the legs or the pelvis or occasionally in the aorta. (234 cases only had x-ray study of arteries.)

The most striking fact brought out in Table 2 is the influence of the long duration of diabetes upon the incidence of calcified arteries. The second interesting

TABLE II

282 CASES OF DIABETES WITH ONSET BETWEEN 15-30 YEARS OF AGE

Duration Diabetes Years	Cases Number	Average Age Per Cent	Hypertension Per Cent	Elevated Capillary Fragility Per Cent	Retinitis Per Cent	Retinitis Proliferans Per Cent	Coma 1 or more times Per Cent	Nephritis Per Cent
0-9	90	27	2	10	4	0	20	6
10-19	131	38	34	57	50	2	29	25
20-29	61	48	38	67	60	6	25	22

Duration Diabetes Years	Cases Studied Number	Calcified Arteries Per Cent
0-9	71	21
10-19	107	66
20-29	56	88



point is that, in the patients whose diabetes is less than 10 years' duration, in the eye grounds only small deep hemorrhages were found. Flame-shaped hemorrhages and exudates did not appear until the duration of diabetes exceeded ten years and, indeed, until the hypertension had become a more significant feature. Retinitis proliferans also was a late development.

increase in the frequency of calcification of moderate and severe degrees. Between five and ten years duration small traces of calcification were present in 79 per cent of the patients who showed calcification. These small traces were present only in 24 per cent of the patients with a duration of 20 to 29 years. Four plus calcification, which was present in only 3 per cent of

TABLE III  
RELATION OF ARTERIAL CALCIFICATION OF PELVIS AND LEGS TO DURATION OF DIABETES

Duration Diabetes Years	Cases Number	Location of Calcification		Cases with Calcification Number	Extent of Calcification		
		Pelvis Per Cent	Legs Per Cent		Trace to 1+ Per Cent	2+ and 3+ Per Cent	4+ Per Cent
0-5	35	3	0	1	100	0	0
5-10	36	14	36	14	79	21	0
10-15	54	28	56	33	52	45	3
15-20	53	42	70	38	55	37	8
20-29	56	73	82	49	24	53	23

In Table 3 is summarized the data dealing with the relation and extent of arterial calcification in the pelvis and legs and the duration of diabetes.

In the group of thirty-five cases with diabetes of less than five years in this age period only one patient showed a trace of calcification in the pelvic arteries even with the most meticulous technique in carrying out roentgenograms of the legs, the pelvis and aorta. Thirty-six cases with duration of diabetes between five and ten years showed small amounts of calcification in the pel-

vis and the patients with diabetes of ten to fifteen years' duration, was present in 23 per cent of the patients with duration of 20 to 29 years.

The great increase in the frequency and extent of calcification in these vessels leaves no doubt about the relation of the duration of diabetes to its incidence. However, another factor must also be considered, that is, the control of the diabetes. Here again one must be reminded that as the duration of diabetes increases, the groups of patients under consideration more and more

TABLE IV  
RELATION OF CONTROL OF DIABETES TO DEVELOPMENT OF RETINITIS AND ARTERIAL CALCIFICATION AFTER TEN OR MORE YEARS OF DIABETES

Duration Diabetes Years	Cases Number	Poor Control Cases No. Per Cent		Retinitis Cases Per Cent	Calcification Cases Per Cent	Fair Control Cases No. Per Cent		Retinitis Per Cent	Calcification Per Cent
		No.	Per Cent			No.	Per Cent		
10-19	121	76	58	65	78	55	42	29	62*
20-29	61	38	62	90	96	23	38	18	65

\*X-rays lacking in seven cases

Duration Diabetes Years	Cases No.	Poor Control Cases No. Per Cent		Nephritis Cases Per Cent	Fair Control Cases No. Per Cent		Nephritis Cases Per Cent
		No.	Per Cent		No.	Per Cent	
10-19	121	76	58	40	55	42	7
20-29	61	38	62	26	23	38	3

vis in 14 per cent and in the legs of 36 per cent of the patients. Calcification in this age group was extremely slight as indicated by the fact that in 79 per cent it was recorded as a trace to one plus. As each period of the duration of diabetes increases the percentage of patients showing calcification of the arteries of the legs and the pelvis steadily increases. It is notable that calcification in the legs is by far the most frequent and the earliest location of calcification. As the duration of diabetes lengthens there is a marked corresponding

fail to include those patients who have dropped out of the group by reason of death from coma, vascular disease or other reasons. It is notable, therefore, that errors are likely to be made on the side of minimizing the importance of lack of control of the diabetes. Those patients with the most serious lack of control have died along the way and are no longer included in the group we are studying. With this comment, attention is directed to Table 4, in which the relation of the degree of control of the diabetes to the development of

TABLE V  
INCIDENCE OF NEPHRITIS IN RELATIS IN DIABETES OF LONG DURATION  
51 CASES OF NEPHRITIS AMONG 282 PATIENTS

Duration Diabetes Years	Cases Hypertension	Retinitis With Increased Capillary Fragility Per Cent		Retinitis With Normal Capillary Fragility Per Cent	Increased Capillary Fragility Without Retinitis Per Cent		Retinitis Normal Cases Per Cent
		Per Cent	Per Cent		Per Cent	Per Cent	
10-29	66	77	71	6	9	14	

retinitis, arterial calcification and nephritis in cases of long duration is made. The cases under ten years' duration are not included in this table, because in them the incidence of these complications are so low.

It is seen that among the patients with duration of ten to nineteen years, numbering 131 cases, poor control was present in 58 per cent. In this group retinitis was found in 65 per cent, calcification in 78 per cent, and nephritis in 40 per cent. Among the 61 patients whose duration was 20 to 29 years, poor control was

in diabetic patients without hypertension, usually hypertension does develop before many years have passed. Table 5 shows the relation of hypertension, retinitis and increased capillary fragility in patients with diabetes of long duration.

In 192 patients whose diabetes had a duration of from ten to twenty-nine years were 66 patients or 34 per cent with high blood pressure. The fact that 34 per cent of 192 patients developed blood pressure exceeding 150mm. mercury after ten years duration is striking,

TABLE VI  
ASSOCIATION OF  
RETINITIS AND CAPILLARY FRAGILITY IN DIABETES OF LONG DURATION

Diabetes Duration	Cases	Retinitis With Increased Capillary Fragility	Retinitis Without Increased Capillary Fragility	Increased Capillary Fragility Without Retinitis
Years	Number	Per Cent	Per Cent	Per Cent
10-29	127	71	10	19

present in 62 per cent and here the incidence of retinitis had risen to 90 per cent, calcification to 95 per cent and nephritis was 26 per cent. The striking difference appears, however, when we compare with this group those patients whose diabetic control is classified as fair. In the poorly controlled, ten to twenty year duration group, retinitis was present in 65 per cent of the cases as compared with an instance of only 29 per cent retinitis in the fairly controlled group. In the twenty to twenty-nine year duration group, 90 per cent of the poorly controlled patients now showed retinitis while in the group with fair control of twenty to twenty-nine years duration, only 18 per cent showed retinitis. Even calcification of the vessels in the group of long duration was present in only 65 per cent of the group with fair control, whereas 96 per cent of the group which had been poorly controlled showed calcification of the vessels. The difference in incidence of nephritis between the groups is also striking. In the ten to nineteen year duration group with fair control, only 7 per cent of the patients developed nephritis, as compared to 40 per cent in the poorly controlled cases. In the twenty to twenty-nine year duration group with fair control, 3 per cent of these patients had nephritis while 26 per cent of the poorly controlled patients in this same duration group had it. This table then shows a striking difference in the incidence of complications such as retinitis, nephritis and calcification which is dependent upon the degree of control of the diabetes. In Table 4 also appears a very striking finding, namely that of twenty-three patients with duration of diabetes between twenty and twenty-nine years with fair control, nineteen of these cases did not show any retinal hemorrhages. It is seen that in this group eye ground examinations were carried out by experienced ophthalmologists in 100 per cent. Actually, there were twenty cases of over twenty year duration without retinal hemorrhage. These twenty cases have all taken insulin and on the average insulin was taken in 93 per cent of their diabetic lives.

Formerly the belief was held that no retinal hemorrhages occurred without hypertension and arteriosclerosis. Later studies indicated that in patients with diabetes of long duration retinal hemorrhages were fairly common even before hypertension had developed. It is true, however, that although retinitis may occur

in view of the fact that this group is made up of young people. When this series is analyzed in Table 5 it appears that of these 66 cases 51 had retinitis. Forty-seven had retinal hemorrhages with increased capillary fragility and 4 cases had retinal hemorrhages without increased capillary fragility. In six patients both hypertension and increased capillary fragility were present without hemorrhages and in three cases hypertension was not accompanied with retinal hemorrhages or increased capillary fragility.

The association of retinal hemorrhages and increased capillary fragility is shown in Table 6 which shows that among 127 cases with diabetes from ten to twenty-nine years in duration a total of ninety cases or 71 per cent had retinitis with increased capillary fragility. In thirteen cases retinal hemorrhages occurred without any increase in capillary fragility and in twenty-four cases an increase in capillary fragility was not associated with any retinal hemorrhages. It is evident that an increase in capillary fragility is an early evidence of a generalized change in the capillary wall. The fact that it is a generalized change is not often commented upon. Thus our attention tends to be centered upon the retina. Actually, in the retina there is increasing evidence that the small venules play an important role in the retinal picture. In these cases, when increased capillary fragility alone has been observed, in many instances it has been followed within a moderately short period by the development of retinal hemorrhages or albuminuria.

The cause of death has been nephritis in 14 per cent of 310 deaths of patients whose diabetes began between 15 and 30 years of age. Table 7 summarizes the data dealing with the incidence of nephritis in relation to the duration of diabetes. Among ninety cases with diabetes of less than ten years duration (average age 27 years) there were only five cases of nephritis or 6 per cent. Of the 129 cases with a duration of diabetes between ten and nineteen years (average age 38 years) thirty-two cases or 25 per cent had nephritis. As the duration of diabetes increased to from twenty to twenty-nine years (average age 48 years) the incidence of nephritis decreased, since only fourteen cases out of a total of sixty-six had nephritis—an in-

TABLE VII  
INCIDENCE OF NEPHRITIS IN RELATION TO DURATION OF DIABETES  
51 CASES OF NEPHRITIS AMONG 282 PATIENTS

Duration Diabetes Years	Total Cases	Nephritis	
		No.	Per Cent
0-9	90	5	6
10-19	131	32	25
20-29	61	14	22

Duration Diabetes Years	Nephritis Cases Number	Proteinuria Per Cent	Hypertension Per Cent	Retinitis Per Cent	Edema Per Cent	Azotemia Per Cent	Anemia Per Cent	P. S. P. below 55% Per Cent
0-9	5	100	0	40	20	0	0	0
10-19	32	100	75	81	53	28	34	41
20-29	14	100	80	80	71.4	71.4	73	55

cidence of 22 per cent. When the entire series of 282 cases Table VII is taken it is seen that there were fifty-one cases of nephritis, an incidence of 18 per cent. This figure corresponds with that of Kimmelsteil and Porter (7) who reported an incidence of 17 per cent of nephritis in all cases of diabetes. They stated that it was two times as common in women as in men. However, that is not in agreement with the sex incidence in this series since twenty-six were males and only twenty-five were females, which is in keeping with the sex incidence of diabetes in young people. (8)

Hypertension was not found in any case of nephritis with duration of diabetes under ten years. However, twenty-four out of thirty-two cases or 75 per cent with duration of diabetes from ten to nineteen years had hypertension, with the duration of diabetes from twenty to twenty-nine years, hypertension was present in 80 per cent of the cases. Rifkin, et al, (9) found an incidence of hypertension in 95 per cent of their cases. The apparent discrepancy here is due to the fact that some of the patients reported in this series were seen in the early stages of their nephritis before hypertension developed.

Retinitis appeared relatively early in the disease since 40 per cent of the cases with less than ten years of diabetes showed retinal hemorrhages. The incidence rose to 81 per cent in these cases with diabetes between ten and nineteen years duration and was 80 per cent in those with diabetes between twenty and twenty-nine years duration.

Edema was present in only one case of nephritis with duration of diabetes under ten years. Fifty-three per cent of the cases with duration of diabetes between ten and nineteen years had edema, while 71 per cent with over twenty years had edema. It can be seen from these figures, therefore, that edema is not necessarily present in diabetic nephritis, especially during the early stages of this disease.

Azotemia is a late manifestation of the disease and was not present in any of the cases of nephritis with diabetes of less than ten years duration. Only 28 per cent of the cases with duration of diabetes between ten and nineteen years exhibited nitrogen retention. The influence of the duration of diabetes on the severity of nephritis is clearly seen when the diabetes has been present over twenty years, for then the occurrence of azotemia was 71 per cent.

Anemia was not found in any of the cases of nephritis with diabetes under ten years duration. Thirty-four per cent of the patients with a duration of diabetes from ten to nineteen years had anemia, while the incidence of anemia increased to 73 per cent in those patients with diabetes of over twenty years duration. This seems to indicate that the development of anemia roughly parallels the degree of disturbed kidney function as indicated by the presence of nitrogen retention.

Kidney function was measured by the phenolsulfonphthalein test, using 1 cc. of the dye and collecting the urine at the end of one hour and two hours. All of the cases with diabetes of less than ten years duration eliminated over 60 per cent of the dye. Out of twenty-two cases with duration of diabetes between ten and nineteen years, nine cases or 41 per cent eliminated less than 50 percent of the dye in two hours. Five out of nine cases, or 55 per cent, with duration of diabetes of over 20 years, excreted less than 50 per cent of the dye, the lowest value being 8 per cent in a patient with advanced renal disease.

Hypercholesterolemia (over 250 mg. per cent) was found in one patient with diabetes under ten years duration. Ten patients out of twenty-two or 45 per cent had hypercholesterolemia when the duration of diabetes was between ten and nineteen years, and the incidence rose slightly higher when the diabetes had been present over twenty years, for then there were five out of nine cases, or 55 per cent.

The most significant urinary finding in patients with diabetic nephritis is the presence of proteinuria. All fifty-one cases exhibited this. It is the first objective evidence of nephritis and is present throughout the course of the disease, although in its very early stages proteinuria may be intermittent in nature.

Hematuria, microscopic or gross, is rare until the disease is far advanced. No patient with nephritis whose diabetes was less than ten years duration had any red cells in the urinary sediment. Only 37 per cent of patients whose diabetes had been present between ten and nineteen years had any red cells in the urine and in the greatest majority of them, they were reported as rare, occasional or 1-2 per high powered field. The incidence of microscopic hematuria, however, was slightly higher in those patients with diabetes for more than twenty years. Here it was present in 43 per cent of the cases.

Cylindruria is also relatively infrequent. Here again

none of the patients with diabetes of less than ten years duration had any casts in the urinary sediment. When the duration of diabetes was between ten and nineteen years, 28 percent of the cases had either hyaline or granular casts or both in the urinary sediment. The incidence is about the same in those cases with a duration of diabetes of over twenty years, for here it was 29 percent. Casts were found only in the urinary sediment of patients with the fully developed picture of nephritis and usually in the advanced stages.

#### DISCUSSION

The role played by the duration and inadequate treatment of diabetes in the genesis of premature vascular disease, nephritis, retinitis and coronary sclerosis in young diabetes is increasingly recognized. Root and Warren (10) commented upon these complications in the first Deaconess Hospital autopsy series and the subject of arteriosclerosis in diabetes received special consideration by Joslin (11) in 1928 in reviewing causes of death in a follow-up of a large series. Although the mechanism of production is still uncertain, the relation of these lesions to poor control of diabetes is increasingly evident in a recent series of 110 diabetic post-mortem. Rabinowitch (12) comments upon diabetic retinitis, deaths from nephritis and even coronary thrombosis in cases of juvenile diabetes where treatment has not been followed carefully.

The most striking finding in the present series of cases was the relation of the degree of control of the diabetes to the development of retinitis and calcification of the arteries and nephritis. When the duration of the diabetes then is considered along with the degree of control of the diabetes then the difference in the incidence of retinitis and calcified arteries is even more significant. Among patients surviving more than twenty years of diabetes 90 per cent of those who had maintained poor diabetic control developed retinitis, while of those who had maintained fair control only 18 per cent developed retinitis. Similarly, 96 per cent of the former exhibited calcified arteries while only 65 per cent of the latter showed x-ray evidence of calcified arteries. These figures point definitely to the important role which is played by these two factors in the development of premature vascular disease in diabetes and which as yet have not received proper emphasis.

Hart (13) concluded from an anatomical study of forty-five patients with diabetes of five or more years duration that the duration of diabetes is not a "positive factor in the production of arteriosclerotic changes." He makes a similar statement concerning the combined factors of age and duration of diabetes in the production of arteriosclerosis. However, he does not mention the factor which seems to be most important when considered along with the duration of the diabetes, namely, the degree of control of diabetes. Ricketts (14) in discussing the vascular disease in diabetes believes that long continued poor control of the diabetes "will prove to be at least one of the factors involved" in the etiology of arteriosclerosis in diabetes. This present series of cases shows definitely that the incidence of retinitis and calcified arteries is much greater in those cases who had maintained poor control of their diabetes as compared to those who maintained fair control.

Since 1936 when Kimmelstiel and Wilson (15) reported a series of eight cases of diabetic nephritis which they termed intercapillary glomerulosclerosis, many reports have appeared discussing the clinical aspects of the disease, (9) the pathological changes involved in the kidney, (16) the specificity of the glomerular lesions (7) and the frequency of the syndrome (7). Most reports stress the greatest incidence of the disease as occurring in the 6th and 7th decades of life, (9, 17) yet White and Waskow (18) have shown that every diabetic child at the George F. Baker Clinic who survived fifteen years of diabetes and came to autopsy showed this lesion. This present series of 282 cases of diabetes with onset between fifteen and thirty years of age revealed definitely that the incidence of diabetic nephritis (diabetic glomerulosclerosis) paralleled the duration of the diabetes and not the age of the patient. Under ten years of diabetes the incidence of nephritis was 6 per cent, rising to 25 per cent with diabetes between ten and nineteen years, and being 21 per cent in patients with diabetes of over twenty years duration. The percentage decreased slightly in the twenty year duration cases because many of the patients died before living this long with their diabetes since the onset of nephritis usually occurs after ten to fifteen years of diabetes and progresses on to death in an average of six years from the time of onset of nephritis (19). This is in complete disagreement with Laipply et. al (17) who stated that there was no significant correlation between the degree of development of intercapillary glomerulosclerosis and the duration of diabetes. These same authors also stated that "the histories reveal no demonstrable relation between the specific treatment of diabetes and the development of the renal or pancreatic lesions." It is important to realize that their pathologic study included among 122 cases of diabetes only four patients under forty years of age. Eighteen were from forty to forty-nine years of age, ninety-four cases were between fifty and eighty years of age and six cases were between eighty and eighty-nine years of age. It is well known that histories of duration of diabetes in patients over fifty years of age commonly err by understatement. That is, the diabetes has usually existed for some years. Two or 50 per cent of their four cases under forty years of age had the lesion. Indeed, they point to the fact that their only juvenile case, aged sixteen years with diabetes for ten years, had no hypertension or vessel arteriolar arteriosclerosis, suggesting the lesion may be due to diabetes alone. Their paper gives no details about the character of treatment upon which a judgment may be based. Actually Table 6 (p. 360) of the article by Laipply, et. al (17) shows that the typical glomerular masses did not occur in diabetes of less than one year's duration and increased in frequency as the duration of diabetes increased. Practically all of our patients were first observed within 2 years after the onset of diabetes and followed through the clinic at varying intervals for as long as twenty-nine years in some cases. Therefore, it was possible to follow the clinical evolution of the nephritis and note the order of appearance of the various clinical signs of nephritis.

Most reports (9) stress that intercapillary glomerulosclerosis occurs most frequently in patients with mild diabetes, yet in this series 85 per cent of the patients

with nephritis required from 30 to 112 units of insulin per day for good control. The degree of control of the diabetes is an important factor in the development of nephritis. Sixty-seven per cent of the patients with nephritis in this series had maintained poor control of the diabetes. Of the patients who had maintained fair control of their diabetes only 22 per cent developed nephritis. Striking evidence in this respect is found in the fact that in the twenty-four months ending June 1, 1950 twenty patients have been awarded the Victory medal. This award is made to patients who have had diabetes for twenty-five years and who show no evidence of arteriosclerosis, retinitis, hypertension, albuminuria or nephritis as determined by x-rays of the aorta, pelvic arteries and legs, as well as examination by an ophthalmologist and internist.

The most constant sign of nephritis was proteinuria both in our series and in Rifkin's (9) cases. Laipply, (17) however, stated that 7 per cent of the patients with glomerular lesions had no albuminuria. He does not state whether more than one urine specimen was examined or at what stage of the disease the urine was examined, if at all. In nine of their cases there were no urine reports available. The onset of proteinuria in this series varied from four years to twenty-one years after onset of diabetes. The patient who developed proteinuria after only four years of diabetes, case No. 20332, had her onset of diabetes in 1940 at the age of 17, diabetic coma in January 1941, September 1942, January 1943 and acidosis in September 1943 before she developed albuminuria at the age of 21. Edema appeared soon afterwards and at the time of study in December 1948, the fundi showed no hemorrhages or exudates, capillary fragility was normal, blood pressure was 120/80, N.P.N. was 26 mg. per cent, cholesterol was 488 mg. per cent, serum protein was 4.5 grams per cent, urine had a specific gravity of 1.030, albumin 225 mg. per cent, sediment revealed 1-2 wbc/hpf, no red cells and no casts. Phenolsulfophthalein excretion was 70 per cent at the end of two hours. X-ray failed to reveal any arterial calcification. She required 22 units of crystalline insulin and 40 units of protamine zinc insulin daily. Here is a patient who shows the consequences of poor control of diabetes with a resultant early onset of the clinical signs of nephritis.

In contrast, case No. 10742, did not develop albuminuria until after twenty-one years of diabetes. This patient was eighteen years of age in 1927 at which time he developed diabetes. He did not begin insulin until 1932 at which time he developed diabetic acidosis as a result of dietary indiscretions. This was his only episode of acidosis although he maintained only fair control of his diabetes. Twenty-one years after onset of his diabetes he developed albuminuria and within six months he entered the hospital for study in February 1949. At this time his blood pressure was 220/104, capillary fragility showed 250 petechiae, fundi revealed many punctate hemorrhages and waxy exudates, and he had periorbital edema as well as 2 plus pitting edema of the lower extremities. The NPN was 77 mg. per cent, serum protein was 4.4 gm. per cent, cholesterol was 435 mg. per cent, hemoglobin 11.9 gm. per cent, RBC 3,900,000 and the P.S.P. excretion was 31 per cent at the end of two hours. The urine had a specific gravity of 1.016, albumin 530 mg. per cent and the sediment

revealed 3-4 RBC/hpf, 6-8 WBC/hpf and 10-12 casts. These two cases are presented in detail because they exemplify the influence of the degree of control of the diabetes in accelerating or retarding the onset of the clinical signs of diabetic nephritis. These two factors, duration and control of diabetes, have not been given proper consideration when discussing the etiological factors involved in diabetic nephritis. Too much has been said concerning the severity or mildness of the diabetes as measured by insulin dosage which bears less relationship to the development of nephritis than more important factors, namely duration of the diabetes and degree of control of the diabetes. The latter factor appears to be the more important of the two in this series, since many patients developed clinical signs of nephritis after only four to six years of diabetes when poorly controlled, while others developed signs only after twenty to twenty-one years of diabetes when the diabetes was fairly well controlled.

One factor which has received little attention in previous reports on diabetic nephritis, but which bears a definite relationship to the clinical manifestation of diabetic nephritis is the influence of the toxemia of pregnancy. In this series two patients occurred in whom the first clinical evidence of nephritis was observed during the course of pregnancy. In both instances albuminuria, hypertension and edema appeared for the first time during pregnancy, and persisted following the end of pregnancy. Both were delivered of live babies. However, even in these cases, the factor of control of the diabetes was important, since both patients had at least two episodes of acidosis prior to the onset of their nephritis. One patient, case No. 12203, died at the age of thirty within two years after the onset of her nephritis in uremia and at autopsy, the typical lesion of diabetic glomerulosclerosis was found as well as generalized arterio and arteriolar sclerosis.

Rifkin, Parker, Polin, Berkman and Spiro (9) have given a detailed clinical and pathologic description of the fully developed syndrome of diabetic glomerulosclerosis. They also point out the fact that hypertension, edema and retinitis were present in the majority, but not all cases. They were unable to correlate the degree of control of the diabetes and the development of glomerulosclerosis due possibly to the short period of observation of the patients and to the difficulty of obtaining adequate histories and clinical records of treatment prior to the onset of nephritis. Much of the confusion concerning the various aspects of glomerulosclerosis is due to inadequate data concerning the control of the diabetes prior to the onset of nephritis, and only when cases are closely followed up in this way, paying particular attention to the duration and degree of control of the diabetes and correlating these with the appearance of the various manifestations of the syndrome will a clear cut understanding of this syndrome ensue.

#### SUMMARY

1. The incidence of vascular lesions in the kidneys, retinae and peripheral vessels of 282 patients with onset of diabetes between 15 and 30 years of age has been studied with special reference to the duration of diabetes and the character of control of diabetes.

2. The character of control of diabetes was con-



sidered poor when coma had been present one or more times, blood sugar values and urine tests have been abnormal when medical examinations have been infrequent and when the use of insulin had not been begun within a year of onset of diabetes. Fair control implied the early use of insulin, cooperation on the part of the patient in carrying out urine tests frequently and having fairly regular blood and urine tests with examinations by a physician. Exceptional control occurred in only a few medial cases not included in this series.

3. The incidence of retinal lesions including retinitis proliferans in patients observed over 20 year period was much reduced in those patients with fair control in contrast with those patients with poor control.

4. X-ray evidence of calcification of peripheral vessels or of the pelvic vessels increases with duration of diabetes and with lack of diabetic control.

5. Nephritis occurred in 51 cases of this series but in only 5 instances did it begin before the tenth year of diabetes. Inter-capillary glomerulosclerosis is more common and more malignant in young diabetics of long duration than in later life. It is therefore related to severity of diabetes.

6. Only slight traces of calcification in arteries occurred in 24 per cent and none was present in 12 per

cent of 56 patients with diabetes of 20 to 29 years duration.

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## THE SARCOMAS OF THE STOMACH: A REVIEW WITH REFERENCE TO GROSS PATHOLOGY AND GASTROSCOPIC MANIFESTATIONS

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THE sarcomas of the stomach have been considered to be, for all practical purposes, undiagnosable prior to histopathologic study. Although there have been reported a few cases in which a correct clinical diagnosis was followed directly by radiation therapy and a subsequent good therapeutic result, by far the majority of preoperative diagnoses have had to be considered speculative, pending surgical investigation. There is some evidence that the more general use of the flexible gastroscope has permitted more accurate diagnoses, but the situation remains, of course, far from good. The gastric sarcomas are uncommon enough so that gastroscopic experience with them has been small. The individual examiner encounters one so infrequently that he is loath—or perhaps fearful—of suggesting the diagnosis in a situation where error could lead to disastrous results. Only to the tyro is gastroscopic differentiation of the gastric tumors easy.

The experiences of skilled gastroscopists and other clinicians have led to a wide range of recorded opinion regarding the potential diagnostic help afforded by the gastroscope in the diagnosis of sarcoma. In 1942 O'Donoghue and Jacobs (86) stated: "We believe that the greatest aid in making a diagnosis earlier will come through advancement of gastroscopic study . . ." In his textbook in 1937 Schindler (112) indicated that at times the gastroscopic picture is "characteristic and cannot be mistaken for any other picture." Yarnis and

Colp (138) in 1943 stated, "Gastroscopy may prove of definite diagnostic value especially in identifying the diffusely infiltrating type with numerous submucosal tumors. . . . However it is almost impossible to differentiate the ulcerative or localized polypoid tumors from other malignancies of the stomach. . . ." Renshaw and Spencer (106) admitted, "At one time one of us thought the gastroscopic appearance of lymphosarcoma was distinctive, but with further experience we do not believe the diagnosis can be made with any degree of certainty." In another communication (122) they added, "From (our) experience it must be concluded that the diagnosis of sarcoma of the stomach can not be established by gastroscopic examination alone. No constant or even frequent appearance can be classified as characteristic of gastric sarcoma." Carrying the matter to a finer point, Bassler and Peters (6) stated, "It is generally accepted that the cytologic and embryologic variations of sarcoma present no distinctions clinically; indeed, it probably always will be impossible to make a diagnosis of gastric sarcoma with qualification as to its cellular structure." Illustrative of the gastroscopic difficulties involved is the group of 22 gastroscopied patients reported by Bassler and Peters (l.c.) and Spencer, Collins and Renshaw (122); here the correct endoscopic diagnosis of sarcoma was made in only eight, or 36 percent.

The following material was collected in an effort to elucidate common peculiarities of the gross forms of the different types of gastric sarcoma, and to gather

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and outline gastroscopic findings in these diseases as they have been reported to date. Some previously unpublished cases are presented briefly to illustrate the gross anatomic types. Time is not yet ripe for formulation of endoscopic criteria for diagnosis. It is proposed, nevertheless, that it may be helpful to bring together gastroscopic experiences which have been reported to date, as a basis for critical consideration for future diagnostic thought. Isolated case reports in themselves do not help the gastroscopist much, but collected reports may permit a degree of definite thought. With the gastroscopic method's maturation, there must be closer scrutiny of its failings, so that it may be utilized with full confidence.

Reports of 124 cases of gastroscopically observed gastric sarcoma have been found in the literature (Table 1). In less than half has there been enough in-

TABLE 1

## REPORTS OF GASTROSCOPICALLY OBSERVED CASES

Histologic type and references	No. cases
Lymphosarcoma: 8, 16, 43, 52, 60, 81, 84, 90, 91, 92, 101, 105, 106, 111, 127, 131, 137, 138, and present communication	26
Gastric leukemia: 50, 93	34
Reticulum cell sarcoma: 24, 81, 86, 138, Hodgkin's disease: 14, 19, 31, 61, 62, 78, 93	4
Hemangioendothelioma: 49	26
Leiomyosarcoma: 6, 89, 91, 114, 118	1
Neurogenic sarcoma: 90	10
Others, reported without diagnosis: 6, 67, 122	1
	22
Total	124

formation supplied to permit the reader to understand the picture which was found. Although it is true that the gastroscopist is able to see considerably more non-artefactual surface detail than is the pathologist, he must, of course, rely on the many reports of resected and autopsy material in order to understand the variations and extremes of the gross tumor configuration. There is included here information gathered both from helpful gastroscopic and pathologic reports. No attempt has been made to include all published cases of gastric sarcoma, because many reports give no data pertinent to the problem at hand. The sarcomas are considered only from angles which may be useful in gastroscopic diagnosis; it is felt that review of certain information regarding incidence, histologic classification, and relative frequency of localizations within the various portions of the stomach, as well as of that pertaining directly to gross form, is required for this purpose.

## INCIDENCE OF THE GASTRIC SARCOMAS

Madding (72) calculated that 423 cases of primary gastric sarcoma had been reported through the year 1937, and it was the opinion of O'Donoghue and Jacobs (86) that less than 500 cases had been recorded through 1944. Of more help than the total number of reported cases is the relative incidence of the tumor as compared with certain homely statistics. Among 12,673 collected cases of all types of gastric malignancy, 148 cases of gastric sarcoma were found (Table 2). Seven were diagnosed at New York Hospital among 149,469 consecutive general hospital admissions between 1933 and 1942 (81). Combining the figures of O'Donoghue and Jacobs (86), Borrmann (12), Hesch (55) and Tilger (128), it is found that 18 cases of gastric sarcoma were discovered during 40,244 consecutive routine autopsies. Fourteen cases of primary

TABLE 2  
REPORTED INCIDENCE OF GASTRIC SARCOMA AS COMPARED WITH ALL TYPES OF GASTRIC MALIGNANCY (SURGICAL AND/OR AUTOPSY DATA)

Reference	Clinic	Years included	No. Cases gastric malignancy	No. cases gastric sarcoma
Cameron and Broslich (21)		7 years	137	2
Pack and McNeer (88)	Memorial Hosp., N. Y.		400	5
O'Donoghue and Jacobs (86)	Cook Co. Hosp.	1930-1940	461	9
Cheever (25)	Peter Bent Brigham		628	9*
Yarnis (137)	Mount Sinai Hosp., N. Y.	1933-1940	1035	12*
Balfour and McCann (5)	Mayo Clinic	1908-1928	4159	47
Spencer et al. (122)	Cleveland Clinic	1921-1944	1220	19
Warren and Lulenski (132)			569	14**
Marshall and Aronoff (75)			464	15
Counsellor et al. (29)	Mayo Clinic	1944	298	10
Schroeder and Schattenberg (116)	Charity Hosp., New Orleans	1906-1941	1313	13
Borrmann (12)			245	5
Lubarsch (70)	Berlin		2747	9
Hünemann (57)			238	7
McSwain and Beal (81)			391	7
Kreitner (63)			74	5*
		Totals	12073	148

\*Lymphosarcoma only; not included in totals.

\*\*Primary solitary malignant lymphoid tumors only; not included in totals.

gastric sarcoma were found among 2,672 patients with sarcoma of any region of the body (30, 48, 53, 116, 135).

## HISTOLOGIC CLASSIFICATION OF THE GASTRIC SARCOMAS

The following classification of the gastric sarcomas is suggested for present purposes. Its main attribute is that of completeness. The disadvantage is that it is far more useful as a guide to didactic thinking than as a practical help in diagnosis or prognosis. The many histologic classifications to be found in the literature indicate the pathologist's diagnostic difficulties. As previously pointed out (90), however, a variety of classifications does not necessarily indicate histopathologic ignorance, but may serve a useful purpose in emphasizing the complex relationships.

The gastric sarcomas: 1. Lymphosarcomas a. lymphocytic, b. lymphoblastic, c. giant follicular; 2. Leukemic infiltrations, leukosarcomas, and "pseudoleukemia gastrointestinalis"; 3. Reticulum cell sarcomas (retothel sarcoma, retotheliosarcoma) a. stem cell variety, b. blastomycytic variety; 4. Hodgkin's disease a. sarcoma type, b. granuloma type; 5. Plasma cell sarcoma; 6. Angiogenic sarcomas, a. angioblastomas, b. angioendotheliomas, c. angiosarcomas; 7. Leiomyosarcoma; 8. Fibrosarcoma; 9. Neurogenic sarcomas; 10. Myxosarcomas; 11. Others and questionable: liposarcoma; heterologous rhabdomyosarcoma, osteosarcoma and chondrosarcoma; mixed cell types; malignant teratomas; mycosis fungoides.

## RELATIVE INCIDENCES OF VARIOUS HISTOLOGIC TYPES OF GASTRIC SARCOMA

Because of the several histopathologic classifications used by different authors in reporting cases, as well as the varying degrees of histologic specificity, it is not possible to obtain an entirely satisfactory notion of the precise relative incidences of the several histologic types. In Table 3 are compiled figures on 500 cases from many authors, with avoidance of duplication of cases whenever such duplication is evident in the reports.



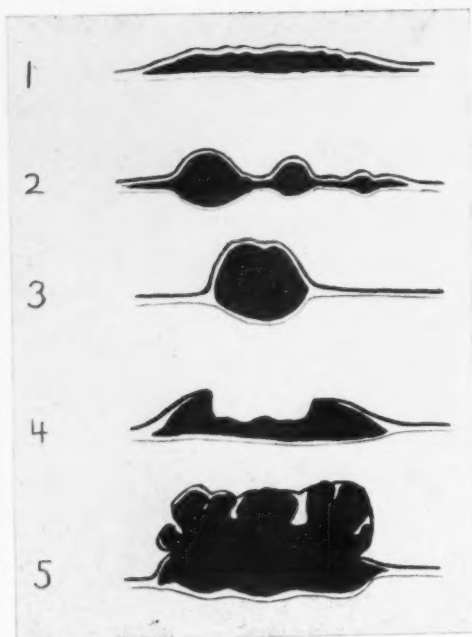


Fig. 1. Schematic representations in cross section of the five gross types of gastric sarcoma.

#### CLASSIFICATION BASED ON GROSS CHARACTERISTICS

Classification based on gross characteristics requires justification. Obviously of importance in understanding the natural history of the tumors, it nevertheless seems rather distant from the problem of tumor identification. Several authors have suggested such a grouping for the pathologist's special purposes, but the matter has not been utilized to any extent in clinical diagnosis. As in the case of the histologic picture, all gradations may be found in the gross types and designation of the extremes of each group must necessarily be rather arbitrary.

There is more to the problem than investigation into fre-

TABLE 3

#### RELATIVE INCIDENCE OF HISTOLOGIC TYPES AMONG 520 COLLECTED CASES OF GASTRIC SARCOMA, EXCLUSIVE OF THE LEUKEMIAS

References: 3, 4, 5, 6, 7, 8, 14, 16, 19, 20, 21, 22, 23, 24, 27, 30, 31, 35, 37, 38, 40, 41, 43, 52, 56, 61, 62, 63, 65, 67, 68, 72, 76, 78, 79, 80, 81, 83, 84, 85, 86, 88, 90, 91, 92, 93, 95, 96, 99, 100, 101, 105, 108, 109, 111, 114, 116, 117, 118, 119, 120, 122, 126, 127, 129, 131, 132, 137, 138.

Histologic type	No. cases	Percentage
Lymphosarcoma	210	42.0
Reticulum cell sarcoma	14	8.8
Hodgkin's disease	45	9.0
Plasma cell sarcoma	4	0.8
Angiogenic sarcoma	21	4.2
Leiomyosarcoma	100	20.0
Fibrosarcoma	13	2.6
Neurogenic sarcoma	6	1.2
Myxosarcoma	0	0.0
"Spindle cell" types	40	8.0
Mixed cell types	2	0.4
Others, unclassified	13	3.0

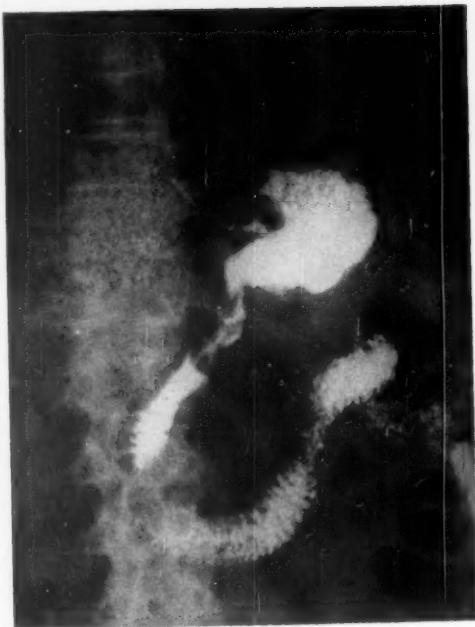


Fig. 2. (Case 1). There is diffuse intramural infiltration of the distal four-fifths of the stomach. At autopsy a lymphocytic lymphosarcoma with a Type 1 gross form was found.

quency relationships between gross form and histologic type. A classification of gross characteristics has no validity if the tumor tends to change its basic form with its progressive growth. Although little is known about the very earliest configurations assumed by the gastric sarcomas, there is some evidence that the tumors tend to maintain their original growth characteristics as they age, in much the same way as do the Borrmann types of gastric carcinoma. The radiologist has good proof of this in the few cases where serial examinations have been possible. It has been common experience for the pathologist at autopsy to find the same gross pattern as the radiologist demonstrated earlier in the disease. Further evidence has been found in a case of plasmacytoma (30) and a case of leiomyosarcoma (89), where, following temporarily successful eradication of the tumors by surgery and super-voltage irradiation, respectively, there was at a later date recurrence of the sarcomas in their original gross form.

The one aspect of the tumor which does change and which tends to present within any gross category considerable variation is ulceration. There is little question that the ulceration of the gastric sarcoma has an ischemic basis. When the tumor overgrows its blood supply, the most distal parts slough. There is, then, a certain correlation between tumor thickness—as opposed to mere lateral extent—and the presence and degree of ulceration. But this is a rather unpredictable matter, for it is well known that at times small sarcomatous projections may show ulceration. The explanation must still be found in ischemia, because, as judged by the appearance of such ulcers and by the known tendency toward suppression of gastric secretory activity in the presence of sarcoma, it is probable that peptic action plays a minor role in the process.

Several classifications based on gross forms are to be found in the literature; some interesting as well as useful approaches to gross pathology are demonstrated. Crouse and DeWitte (22) merely divided the gastric sarcomas into the infiltrating and the circumscribed types. Schlesinger (115) used a classification based on the position of the tumor in relation to the gastric wall: exogastric, endogastric, and infiltrating; to



Fig. 3. (Case 2). Type 3 leiomyosarcoma of the fundus with central ulceration, later removed transdiaphragmatically.

these groups Malenchini and Eoen (74) added a fourth, the fungating type which tends to ulcerate. Levene and Feil (66) have suggested division into a diffuse infiltrating form, a nodular form with multiple nodules invading all of the gastric wall, an infiltrating but limited form, and a pedunculated or sessile tumorous form. The classical discussion of the gastric sarcomas presented by Anschütz and Konjetzny (1) contains a detailed consideration of macroscopic pathology, with this classification: the exogastric sarcomas, made up of the hard pedunculated, the soft or cystic pedunculated, and the soft sessile types; the endogastric pedunculated sarcomas; and the sarcomas which spread through the gastric wall, further distinguished by growth characteristics either as expansive or infiltrative types.

After the cases recorded in the appended bibliography had been reviewed, the following classification was evolved (Fig. 1); it is found to be merely a variation of the groupings as suggested by others, but was formulated with the gastroscopist's special purpose in mind. There was little difficulty in fitting into the various categories the reported cases in which pathologic data was presented, and the classification was felt at the same time to be simple enough to be useful. It is based on gross configuration of the tumor when observed from the mucosal surface only. The largeness of the tumor and its extent of expansion do not influence classification.

#### *A classification of the gross forms of the gastric sarcomas:*

Type 1. Diffusely infiltrating tumor, with an uneven or finely nodular surface but without prominent elevations, with either coarsening or obliteration of the rugal pattern.

Type 2. Infiltrating tumor plaque with a few prominent projecting nodules.

Type 3. Single discrete tumor, sessile or pedunculated, roughly spherical or hemispherical (as governed by its intramural relations), without peripheral infiltration.

Type 4. Ulcerated tumor, with ulcer the most prominent feature, the other earlier gross characteristics having been largely destroyed thereby.

Type 5. Fungating lobulated tumor, usually with multiple shallow ulcerations.

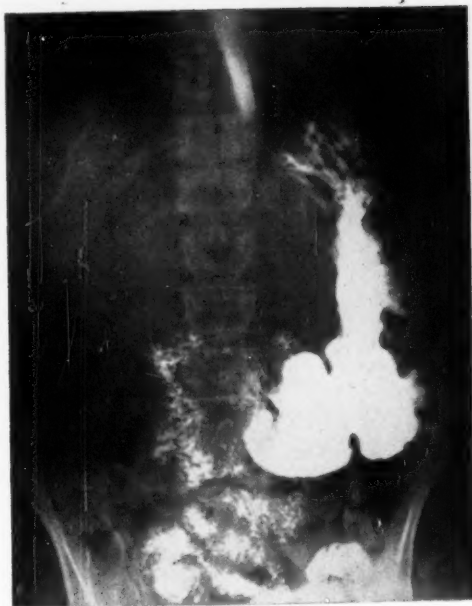


Fig. 4. (Case 3). Type 4 lymphosarcoma of greater curvature of pars media. There is a large ulcer surrounded by an irregular wall.

#### CASES ILLUSTRATING GROSS FORMS

Type 1. Case 1. This 78-year-old white male, a retired judge, was studied because of six months of abdominal pain and a 25 lb. weight loss. Examination revealed extreme emaciation and a large hard epigastric mass. X-ray study (Fig. 2) showed intramural tumor infiltration involving the distal four-fifths of the stomach. Gastroscopy was not done. At autopsy shortly after admission it was found that except for the fundus the gastric wall was heavily infiltrated. The mucosa was intact and entirely smooth, without rugae or nodules. The gastric wall measured up to 3 cm in thickness. There were hepatic metastases. The histologic diagnosis was lymphocytic lymphosarcoma.

Type 2. Two cases (leiomyosarcoma) have already been presented and illustrated (89, 90).

Type 3. Case 2. A 36-year-old white soldier was hospitalized because of brief hematemesis. Examination was normal, but X-ray study (Fig. 3) showed a large spherical intragastric tumor with evidence of ulceration, arising from the subdiaphragmatic portion of the fundus. Gastroscopy was felt to be contraindicated because of the position of the tumor. Trans-thoracic fundusectomy delivered a remarkably symmetrical spherical tumor with a deep central ulcer and an absence of peripheral infiltration. The histologic diagnosis was leiomyosarcoma.

Type 4. Case 3. A 24-year-old white soldier was studied because of right upper quadrant pain and a "seasick feeling" of six months' duration. Examination revealed only evidence of moderate weight loss. X-ray study showed (Fig. 4) an apparently malignant ulcer 3 cm in diameter on the greater curvature of the pars media, surrounded by an irregular filling defect. At gastroscopy a circular ulcer estimated to be 2 cm in diameter was found on the greater curvature toward the distal end of the pars media. The base was smooth and gray, without bleeding. It was surrounded in doughnut fashion by a finely nodular hyperemic wall, with several petechiae. The edge was rough and ill-defined, and the gastroscopic diagnosis was carcinoma. The remainder of the stomach appeared normal. At laparotomy it was found that the greater curvature

and adjacent posterior wall were involved in a tumor process which had begun to invade the pancreas. An anterior gastroenterostomy was done. Biopsy revealed lymphosarcoma, and supervoltage radiation therapy was begun.

**Type 5, Case 4.** A 46-year-old white female died in inanition after a six-month course of melena, weight loss, and epigastric pain. At post mortem examination a rubbery yellow translucent tumor 10x6x4 cm was found fungating from the posterior wall of the pars media and cardia. Its surface had a cauliflower-like coarsely nodulestoned appearance, and was completely free of mucosa. There was blood on the tumor but there was no necrosis or actual ulceration. The stomach was otherwise normal, with a normal appearing mucosa reaching the base of the tumor, and with no peripheral infiltration. The specimen appeared as though a large mass of firm jelly had been applied to the mucosa of an otherwise normal stomach. There were large masses of a similar appearing tumor applied to scattered areas of the peritoneum throughout the abdomen. The histologic diagnosis was myxosarcoma.

#### PREFERENTIAL SITES OF LOCALIZATION OF THE SARCOMAS WITHIN THE STOMACH

Although a well-defined preferential site for the occurrence of the sarcomas within the stomach would be helpful for diagnostic purposes, one must wonder if, when considering such a rare group of diseases as the gastric sarcomas, he should place emphasis on a characteristic which is as far removed from the histologic diagnosis as is the site of growth within the stomach. In actuality, a review of reported cases confirms the suspicion that this factor can be of no help at all in differentiating clinically the sarcomas as a group from other gastric tumors (Table 4). The data in the table

TABLE 4

REPORTED LOCALIZATION WITHIN STOMACH OF 456 COLLECTED CASES OF SARCOMA, IRRESPECTIVE OF HISTOLOGIC TYPE

References: 3, 4, 6, 7, 8, 14, 17, 18, 19, 21, 22, 23, 24, 27, 30, 31, 33, 35, 37, 39, 40, 41, 43, 52, 56, 61, 62, 63, 65, 67, 68, 73, 76, 78, 79, 80, 81, 83, 84, 85, 86, 88, 89, 91, 92, 95, 96, 100, 101, 105, 108, 109, 110, 111, 114, 116, 117, 118, 119, 126, 129, 131, 138.

Region	No. cases	Percentage
Pylorus*	72	15.8
Antrum*	39	8.6
Pars media		
Anterior wall	33	7.2
Posterior wall	67	14.7
Lesser curvature	72	15.8
Greater curvature	70	15.4
Generalized	28	6.1
Fundus	8	1.8
Cardia	10	2.2
Generalized	57	12.5

\*Because of the confusion in the literature regarding the usage of these two terms, one suspects that the true distribution between the two regions may not necessarily be exactly as represented in the figures.

reveal a remarkable trend towards uniform distribution of the tumors throughout the stomach, save for the region of cardia and fundus. The oft-quoted tendency of the sarcomas to avoid the pyloric orifice is seen to be far from correct.

#### CHARACTERISTICS OF THE SARCOMA TYPES

**The lymphosarcomas.** Taylor's (126) succinct description of the simple life history of the gastric lymphosarcomas helps in the understanding of the gross manifestations: "Primary lymphosarcoma of the stomach can arise from any lymphatic tissue in the organ. It is probable, however, that the lesion begins most often in a lymph follicle in the submucosa. From this point of origin, it penetrates along the tissue spaces and

infiltrates the various layers. . . The submucosa is enormously thickened, and this explains the giant rugae. . . The mucosa, not being the site of the original growth, does not show the early characteristic ulceration of carcinoma. However, later ulceration does take place. . ."

The important characteristics of the tumor are summarized in Table 5. By far the commonest histologic type, this group

TABLE 5

DATA ON 80 COLLECTED CASES OF LYMPHOSARCOMA

References: 3, 8, 16, 27, 32, 34, 35, 38, 40, 43, 52, 60, 63, 68, 80, 83, 84, 88, 90, 91, 92, 96, 99, 100, 101, 105, 108, 110, 111, 116, 126, 127, 131, 137, 138.

	No. cases	Percentage
Localization of tumor (73 cases):		
Antrum	24	33
Pars media		
Posterior wall	9	12
Lesser curvature	12	16
Greater curvature	9	12
Generalized	4	6
Fundus	4	6
Generalized	11	15
Gross tumor types (61 cases):		
Type 1	25	41
2	13	21
3	8	13
4	12	20
5	3	4

Gastroscopic features emphasized in the reports (22 cases):

Excess mucus and exudate—7 cases.  
Bleeding from tumor during gastroscopy—8.  
Rugae heavy, thick and rough—10.  
Large deep ulcer with gray base—2.  
Mucosa over tumor:

  normal—1.  
  granular—2.  
  smooth—5.  
  "soft"—1.  
  petechiae—8.  
  erosions—6.  
  yellow-red—2.  
  dark red—5.  
  orange-red—2.  
  gray—2.  
  yellow-gray—2.  
  pale—2.

Mucosa of uninvolved portions:  
  normal—2.  
  pale—1.  
  edema, hyperemia—1.

demonstrates some preference for the antrum and for gross Type 1. The histopathologic subdivisions (lymphocytic, lymphoblastic and giant follicular) show no distinguishing characteristics other than the microscopic ones themselves. The age range among the patients presented in Table 5 was 3 to 80 years, and 65 percent were males.

**Gastric leukemia.** Rarely in leukemia the stomach is infiltrated by significant amounts of the specific leukemia tissue, so that actual gastric tumor is produced. Boikan (11) found gross stomach changes in one of 14 leukemia patients who were studied post-mortem. Mead (82) reported that among 12336 autopsies performed at the University of Minnesota there were 77 cases of leukemia; among these 77, there was specific gastrointestinal infiltration in three. Including in their series those cases in which there was merely microscopic evidence of gastric involvement, Paul and Hendricks (93) reported that 12 of 25 autopsied patients with one of the leukemias showed gastric leukemia. Pearson et al. (94) found definite gross changes in two of 28 autopsied patients, and they reviewed five other cases which had been reported from 1931 to the time of their paper in 1943.

Nonspecific gastric mucosal changes, particularly chronic atrophic gastritis, are frequent in the leukemias. In the experience of Gutzeit and Teitge (59), atrophic changes are especially frequent in lymphatic leukemia, while hypertrophic gastritis outweighs other types in the myelogenous form. The

hemorrhagic tendency of leukemia is, of course, at times manifest in the gastric mucosa (90).

Diagnosis here does not present the problem that it does in the other gastric sarcomas, because the basic disease is general in its manifestations and because in the leukemic patient the question of gastric surgery can rarely arise. The specific gastric changes are generalized, particularly through the submucosa, and the tumors grossly assume only the Type 1 and 2 forms. Paul and Hendricks (93) stated, "In the leukemias one often finds small areas of infiltration and thickening of the mucosa . . . the mucosa may be denuded resulting in ulceration and hemorrhage. At times only small petechial hemorrhages can be found." They pointed out that exaggerations of the rugae occur more often in chronic lymphatic leukemia than in other types, and that this kind of change is usually located near the pylorus. The stomach pictured by Boikan (11) shows enormously thickened rugal convolutions covering its entire surface, with an apparently intact mucosa and a paucity of nodule formation. That illustrated by Palmer (90) demonstrated generalized submucosal infiltration with an abrupt limit just proximal to the pylorus, hard fixed rugae, small nodules, mucosal hemorrhages, and scablike plaques scattered over the surface. Pearson et al. (94) pointed out that the earliest description of the condition, that of Briquet (13), was probably the best; this latter author first compared the appearance of the mucosa in gastric leukemia with that of the cerebral convolutions, and the several specimens which have been described since, as reviewed by Pearson et al., have confirmed the original observation that the Type 1 and 2 forms are characteristic of the disease.

Gastric leukemia has been described gastroscopically by Gutzeit and Teitte (59); there has been, however, some hesitation in the acceptance of their case because no pathologic data were presented and because the findings were somewhat different from what one might expect in the disease. Gastroscopy demonstrated a pale mucosa with spotty hyperemia. On the posterior wall of the fundus there was a large lumped mucosal infiltration, and near by a few pea-sized nodules with white summits. The mucosa was intact. On the greater and lesser antral curvatures there were five polypoid structures covered by hyperemic but undamaged mucosa. There was atrophic gastritis elsewhere in the antrum. Following arsenic and X-irradiation therapy there was regression of the tumors.

Paul and Hendricks (93) reported that from 1941 to 1947 at the State University of Iowa they had gastroscopically observed evidence of leukemic involvement of the stomach in 33 cases. Unfortunately little information was supplied, especially regarding pathologic data, and full acceptance of the specific nature of the described changes is not possible.

"*Pseudoleukemia gastrointestinalis*". This group of diseases constitutes a medical enigma in the historical sense and the term is gradually disappearing from use. Although described as a specific disease entity by Briquet (13) in 1838 and accepted as one after Sternberg's (124) critical review of the subject in 1912, the condition is known to be merely one rather remarkable gross form that many of the histologically distinguishable mesodermal diseases may assume—the lymphomas, other sarcomas, multiple myeloma, Gaucher's disease, von Jaksch's disease, etc. That it is not excessively rare is indicated by the fact that Wells and Mayer (133) in 1904 were able to collect 238 cases. The condition is manifested by massive foreign-cell infiltration of the mucosa of the gastrointestinal tract from cardia to anus. The normal mucosal lymphoid tissue undergoes a tremendous hyperplasia, and the result is gross thickening of the gastrointestinal wall, with a fixed mucosal pattern composed of cerebriform folds. In the patient described by Biggs and Elliott (9), there were in addition many polypoid masses in the stomach. But confusion will be avoided if no attempt is made to classify gross tumor types in "pseudoleukemia gastrointestinalis"; the concept of the condition is useful in indicating that several non-sarcomatous diseases may produce gastric changes which are indistinguishable from true sarcomatous changes.

*Reticulum cell sarcoma.* This tumor, like Hodgkin's sarcoma, leukemic infiltrations and plasmacytoma, is often classified under the lymphosarcomas, a matter which will require histopathologic clarification at some time in the future. But since these tumors are at least microscopically distinguishable and since their antigen is not thought to be the native gastric lymphatic tissue, it may preclude some false confidence in their possible relationships to consider each as a separate entity for present purposes.

The tumors seem to prefer the antral portion of the stomach, and the Type 1 and 2 gross forms (Table 6). The age

TABLE 6  
DATA ON 20 COLLECTED CASES OF RETICULUM CELL SARCOMA

References: 17, 23, 24, 40, 56, 80, 86, 88, 116, 126, 138.

	No. cases	Percentage
Localization of tumor (19 cases):		
Antrum	6	32
Pars media		
Anterior wall	3	16
Posterior wall	1	5
Greater curvature	1	5
Lesser curvature	2	11
Generalized	2	11
Fundus	2	11
Generalized	2	11
Gross tumor types (18 cases):		
Type 1	6	33
2	6	33
3	2	11
4	4	22
5	0	0

Gastroscopic features emphasized in the reports:

Case (86): "confirmed roentgenologic diagnosis" of advanced carcinoma.

Case (24): irregular hypertrophied rugae with flat polypoid nodules of deep white-gray color; large ulcer with necrotic floor.

Case (138): non-distensible tube-like stomach with no mucosal abnormality.

range of the cases presented in the table was 19 to 73 years, and 70 percent were males.

*Hodgkin's disease of the stomach.* Hodgkin's disease rarely involves the stomach, although the occurrence of the specific lesions in this locality has called for considerable scriptive comment. Combining the figures of Symmers (125), Goldman and Victor (45), Paul and Hendricks (93), Jackson and Parker (59), and Burger and Lehman (15), it is found that among 730 cases of Hodgkin's disease there were only nine instances of gastric involvement. Browne and McHardy (14) estimated in 1946 that primary isolated gastric Hodgkin's disease had been reported only 20 times. Farneti (37) in 1947 tabulated 17 proven cases of isolated gastric involvement and 35 additional probable cases. When the gastrointestinal tract is somewhere affected, the stomach is found to be a preferential site; of the 26 collected cases of gastrointestinal Hodgkin's disease reported by Hayden and Apfelbach (51) there was gastric involvement in 13.

Data on 23 cases, seven of whom were gastroscopied, are presented in Table 7. The age range was 27 to 64 years, and 42 percent were males.

TABLE 7  
DATA ON 23 COLLECTED CASES OF GASTRIC HODGKIN'S DISEASE

References: 4, 7, 14, 19, 31, 37, 61, 62, 71, 78, 93, 119.

	No. cases	Percentage
Localization of tumor (23 cases):		
Antrum	5	22
Pars media		
Posterior wall	1	4
Greater curvature	4	17
Lesser curvature	7	30
Fundus	2	9
Generalized	4	17
Gross tumor types (13 cases):		
Type 1	3	24
2	4	31
3	0	0
4	4	31
5	2	15
Gastroscopic features emphasized in the reports (7 cases):		
Excess mucus or gray exudate—2 cases.		
Stomach remarkably distensible despite tumor—1.		
Numerous petechiae over tumor—1.		
No normal mucosa any part of stomach—1.		
Uninvolved mucosa normal—3.		

The general description of the gastric lesions offered by Craver and Herrmann (31) is helpful for diagnostic thinking: "The lesions, which are grayish or pearly white in color, may occur in any part of the stomach. They may be flat, nodular, or in some instances in the form of convolutions somewhat resembling those of the cerebrum. Macroscopically the disease appears as an infiltration with consequent thickening of the gastric wall. It may be limited to a small area or it may be diffuse throughout the whole organ producing an effect similar to linitis plastica. The lesion may be ulcerated and bear a resemblance to a neoplasm." Jackson and Parker (58) divided Hodgkin's lesions in general into three groups: of histologic grounds; they found (59) that only the sarcoma and granuloma types occur in the stomach. They described the sarcoma type as producing large white flat ulcerated tumors often with necrosis and hemorrhage. The granuloma variety, they stated, may occur as polypoid tumors, or broad based ulcers with raised edges, or diffusely infiltrating tumors.

After a thorough review and tabulation of the literature on the subject, Farneti (37) evolved the following classification of the gross manifestations of gastric Hodgkin's lesions: it corresponds fairly closely to Jungmann's (61) grouping, and fits in well with that which is offered here for the gastric sarcomas in general:

1. Ulcerated inflammatory form: coarse rough ulcers, rather large and deep with irregular margins; crateriform, flattened or infiltrated. Base soft and necrotic. May perforate. Surrounding mucosa may be thickened. (Sherman (112) emphasized that infiltration characteristically progresses from the margins of such ulcers, to invade the adjacent tissues).

2. Productive vegetating neoplastic form: single or multiple tumors, very varied in volume and area, white in color. Sometimes hard due to cicatrization, sometimes soft when proliferation and necrosis prevail; in the latter instance ulceration may predominate over the mass, with the formation of deep irregular excavations. Pylorus and lesser curvature usually the sites for this type.

3. Infiltrative hyperplastic form: gastric wall thickened and hard by infiltration of yellow white tissue through the mucosa and submucosa, with enough irregularity of growth to produce nodules. Localized or generalized. May ulcerate. Antropyloric region usually involved.

**Plasmacytoma.** In discussing his case of gastric plasmacytoma, Courret (30) has well emphasized the histopathologic diagnostic difficulties presented by the round cell tumors, and has indicated something of the part that gross morphology must play in diagnosis: "Hence this method (microscopic examination) is not to be depended upon too heavily for arriving at the diagnosis. . . . Had a proper evaluation, at the time of the first operation, been placed on the gross characteristics of the stomach tumor . . . it is probable that the true nature of the condition would have been recognized at that time. Instead, too much reliance was placed on the histologic picture." Because of the rarity of the tumor, information is not available for a reliable judgment of the common gross forms or sites of localization. Apparently only four cases of primary or presumably primary plasma cell sarcoma of the stomach have been reported.

The case of Vasiliu and Popa (130) showed multiple ulcerated nodules of the gastric and intestinal mucosa.

Forsman's (40) patient was a 73-year-old male who roentgenologically presented a circumscribed, broad-based, plum-sized Type 3 tumor arising from the antral greater curvature. Seven and a half years after subtotal resection the patient was well and at work.

In Courret's (30) case of a 48-year-old white woman, gastric resection revealed a stiff, thickened, edematous gastric wall which averaged 1.8 cm in thickness. The rugae were swollen and confluent, and the surface presented in general a lobated appearance. The mucosal surface had lost its velvety appearance, and instead was pale gray with numerous bright red ecchymoses. At a later date the tumor recurred in the gastric stump, and at autopsy it was found that the recurring mass had assumed the same gross characteristics as the original tumor (Type 2).

Schwander, Estes and Cooper (117) reported the case of a 42-year-old Negro male whose stomach upon resection showed a 9x5 cm ulcer surrounding the antrum in an annular fashion. The edges were slightly rolled and hyperplastic, and the firm, gray, irregular base surmounted a diffuse tumor 2 cm thick (Type 4).

**The hemangioendotheliomas.** According to Pendl (95), the hemangioendotheliomas or angioblastic sarcomas may be divided into three histologic groups, the angioblastomas, angioendotheliomas, and angiosarcomas. Experience with the tumors in the gastric locale has been too limited to permit more than a few general statements on the gross manifestations. In 1913 Guisez (49) apparently diagnosed a case endoscopically, but no other gastroscopic reference to the tumor has been found.

The tumors tend to multiplicity in the stomach as elsewhere in the body, are usually either distinctly submucosal or subserosal, although not often pedunculated, and may grow to very large sizes before manifesting malignant propensities. In the case reported by Sherman, Long and Caylor (120) a tumor measuring 20x15x9 cm and weighing 1421 Gm was removed intact from the gastric serosa without disturbing the mucosa. In Pendl's (95) case, an exogastric angioblastoma the size of a man's head was removed, but, after eight years of good health, the patient returned and another tumor of the same histologic type was found growing intragastrically.

Among 16 collected cases (95, 129) of intragastric angiosarcoma, the age range was 28 to 69 years, and males predominated (88 percent). The pylorus was the site of the tumor in 7 percent, the antrum in 33 percent, and the pars media in 60 percent. In this tumor the characteristic gross form is Type 3, and the strict circumscription of the masses is rather remarkable. An infiltrating Type 1 tumor, however, was found in Togni's (129) case, and in collecting 14 additional cases he remarked that the gross form may vary considerably from patient to patient. The mucosa shows an amazing ability to maintain its integrity over the tumor described by Pendl (1. c.), although smooth, contained a flat 6x4 mm erosion.

**Leiomyosarcoma.** In Table 8 are summarized the pertinent

TABLE 8  
DATA ON 28 COLLECTED CASES OF LEIOMYOSARCOMA

References: 6, 21, 33, 40, 41, 65, 76, 79, 80, 88, 89, 91; 96, 114, 116, 118.

	No. cases	Percentage
Localization of tumor (23 cases):		
Antrum	2	9
Pars media		
Anterior wall	6	26
Posterior wall	4	17
Greater curvature	3	13
Lesser curvature	5	22
Fundus	3	13
Gross tumor types (28 cases):		
Type 1	3	11
2	6	21
3	15	54
4	3	11
5	1	4
Gastroscopic features emphasized in the reports (10 cases):		
Mucosa over tumor:		
dark red—1 case,		
very pale—1.		
"soft"—3.		
smooth—6.		
dark creases—1.		
intact—7.		
dull—1.		
increased translucency—3.		
Ulcer—3.		
Uninvolved mucosa:		
chronic atrophic gastritis—2.		
petechiae—2.		

facts in 28 cases of gastric leiomyosarcoma. The age range was 19 to 70 years and 79 percent were males. It is to be noted that about 100 cases of this disease have been published. There are available gastroscopic reports in 10 of these cases.

Two opinions regarding the gastroscopic diagnosis of this tumor may be helpful. Shallenberger and Doane (118) stated, "In the gastroscopic diagnosis . . . generally large polypoid lesions are seen. There may be no ulceration of the mucosa, in fact it is often intact over the lesion. There



is a tendency, however, for many of these lesions to undergo central ulceration which is often very deep, forming almost a 'sinus or fistulous tract'. . . . The differentiation of benign leiomyomas from leiomyosarcomas is made chiefly on the tendency of the latter to grow expansively and to break its natural boundaries and it often ulcerates.' Palmer (89) stated, 'It is felt that the (gastroscopic) diagnosis of leiomyosarcoma should be considered if there are intramural infiltration and smooth hemispheric nodules, underlying an unusually translucent mucosa.'

*Neurogenic sarcoma.* Neri (85) found that 70 cases of benign and malignant gastric neurinoma had been reported between 1922 and 1937. Although he emphasized the potentiality of malignant change and although he felt that 90 percent of malignant neurinomas originate from benign neurinomas, he concluded that only about eight percent of the benign forms undergo malignant change. Malenchini and Roca (74) placed the malignant potentialities of gastric neurofibromas in von Recklinghausen's neurofibromatosis at 13 percent. But the histopathologic features—the cytologic origins and distinction of benign from malignant—are poorly understood in this group of tumors as the careful studies of Goyena, Bianchi and Caeiro (47), Gosset and Bertrand (46), Cornil and Gastaut (28), Canny (22) and others have emphasized. Canney (1. c.) stated, 'The differentiation between benign and malignant tumours . . . depends largely on the cellularity of the tumour and the presence of infiltration of the stomach wall.'

A review of six collected cases (20, 22, 85, 90, 116, 134) revealed a preponderance of males (83 percent) and an age range of 26 to 79 years. The antrum was involved in 50 percent of the cases, the greater curvature of the pars media in 17 percent, and the lesser curvature of the pars media in 33 percent. Among five cases 60 percent demonstrated gross tumor Type 3 and 40 percent Type 4. Apparently gastroscopic appearances are known in only one case (90); here a spherical tumor filled the antrum with bridging rugae rising to the sides of the mass, and the mucosa itself everywhere appeared normal.

*Myxosarcoma.* No report of primary myxosarcoma of the stomach has been found in the literature, although a few textbooks of pathology mention the tumor in this location. In his tremendous experience, Chiari (26) has seen some cases and he has indicated that the Type 5 form may be considered characteristic.

This tumor, in whatever location it may be found, has a strikingly unusual gross appearance as it is seen by the pathologist. Although in the stomach it cannot be distinguished grossly from colloid carcinoma (26), its extreme translucency and yellow jelly-like appearance easily distinguish it from the other sarcomas. Whether this feature might aid in gastroscopic recognition is not known but is thought to be likely, because the mucosa is apparently seldom intact over the tumor.

A previously unreported case recently seen at autopsy, which may have been primary in the stomach, is briefly described above.

#### COMMENT

It is probably fair to state that present day diagnostic techniques, combining clinical, roentgenologic and gastroscopic examination methods, cannot raise the proportion of correct presurgical diagnoses of gastric sarcoma much above the 50 percent mark. Biopsies taken with the help of the flexible gastroscopic aid, probably, cytologic study of gastric contents can be expected to improve results in the future, not only in distinguishing the sarcomas from other stomach lesions, but also in differentiating the histologic sarcoma types. The present communication is intended merely as a review of recorded experiences; it has not been found possible to formulate diagnostic criteria for gross recognition of the sarcoma types. A consideration of the information presented herein reveals that the various sarcomas demonstrate no significant tendencies toward preferential sites of localization within the stomach. Thus, the favored site in no type was selected by more than half of the

individual tumors reported. The preferences for gross tumor forms displayed by the different histologic types were no more distinctive. No characteristics were brought out by study of these features which might be helpful in diagnosis.

The reported local gastroscopic findings themselves—the most direct kind of data now available for the pre-operative diagnosis of the sarcomas—showed a great deal of variation. Thus, in lymphosarcoma the mucosa over the tumor in different patients was found to be yellow-red, dark red, orange-red, yellow-gray and gray. There are two subjective factors which govern the problem here, the failure of the observer to make a detailed record of his findings for the benefit of others, and, frequently, the inability of the gastroscopist to detect just what aspect of a particular lesion it is which plays the determining part in his diagnosis of a tumor type. Because of the lack of detail-uniformity in the reports, validity would be lost with attempts at mathematical evaluation of the collected gastroscopic findings.

It is apparent that the gastroscopic method's potentialities have not been utilized fully in these diseases. Endoscopic help in the future, however, could certainly be more positive if better use were made of past experiences. The rarity of the disease has led almost entirely to single case reports, with the result that numerous observers, with many interests and points-of-view, have recorded their findings in varying degrees of detail. It is forcibly brought out again that a repository for gastroscopic findings, recorded in standardized detail and with pathologic data, in the rarer diseases is a necessity if the diagnostic potentialities of the method are to be realized.

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## ALUMINUM HYDROXIDE AND MAGNESIUM TRISILICATE PLUS MUCIN IN THE TREATMENT OF 125 PATIENTS WITH PEPTIC ULCER

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**E**XPERIENCES with recently available antacids for the use in the medical management of ulcer have repeatedly demonstrated that not one of the older antacid preparations gives sufficient symptomatic relief while being devoid of undesirable side reactions. The search for an antacid preparation which should give prompt symptomatic relief and yet be devoid of side reactions has therefore been going on. The antacid which would be accepted by the clinician as filling the need for an effective therapeutic agent in the treatment of peptic ulcer should possess the following attributes:

1. It should give immediate relief of symptoms during the active stage of the disease.
2. It should prevent or at least decrease the frequency of recurrences.
3. It should promote healing of the ulcer crater as demonstrated by x-ray or gastroscopy.
4. It should be free of side effects, such as *constipation* (produced by the bismuth, calcium or reactive aluminum preparations); *diarrhea* (produced by the magnesium salts); *excessive gas* (produced by the carbonates); *acid rebound* and *alkalosis* (produced by soluble alkali salts).
5. It should be palatable, easily ingested, non-ab-

sorbable and capable of neutralizing gastric acidity to a moderate degree.

6. It should have no effect upon the absorption of various food constituents from the intestinal tract (i.e. amino acids, vitamins, etc.)

The literature contains many reports regarding products which fulfill one or more of the above enumerated properties of a good antacid. In the second decade of this century the soluble alkali alone or in combination with bismuth salts were the sine qua non in the management of peptic ulcer primarily because of their support by the late Sippy (1). These antacids, because of some useful properties, have continued in one form or another to be the treatment of choice in patients with gastro-duodenal ulcer (2). In more recent years, the alkali substances were partly supplemented and partly replaced by the aluminum hydroxide gels (3), and this combination has increased the favorable results obtained with alkalis alone. Shortly after the advent of the aluminum gels, Fogelson (4) advocated gastric mucin as a therapeutic agent. However, neither gastric mucin nor the later prepared vegetable mucin (5) by themselves were improvements over the alkali, the aluminum gels or over the magnesium trisilicate preparations (6), and thus slowly disappeared from the scene. Some more recent introductions, such as the aluminum hydroxide-amino acid mixtures (7), the sodium alkyl sulfate preparations (8, 9, 10), the anion exchange resins (11) and the protein hydrolysates per se (12), have also not fulfilled the criteria for the effective antacid as proposed above.

The reason why some of the more recently introduced

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Fig. 1. Roentgenogram showing large crater on the lesser curvature pars media, just above the angulus.



Fig. 2. Roentgenogram of same patient two weeks after medical treatment, showing decrease in width and depth of the ulcer.

ed substances lag in their popularity with the clinician behind the older products is the more critical evaluation of any new substance at present. While the immediate relief of symptoms in a peptic ulcer patient is a desirable property, it is in the long run a comparatively unimportant one. Occasionally, more important than the healing of the present episode is the duration of the effect—i.e. the absence of recurrences of symptoms while the patient is on a given antacid regime. The yardstick in the evaluation of substances used in the treatment of peptic ulcer is the degree of preventing recurrences.

The prevention of recurrences is now being used by both the clinicians and the surgeons as an index of therapeutic efficiency of any special management of the ulcer patient. As is to be expected, the reports vary greatly, and comparisons of results between various workers are difficult. Since there is no standard method for reporting the results of peptic ulcer treatment according to recurrences, the comparative results of the present individual investigators must be accepted as evidence of the therapeutic efficiency of the particular substance studied.

In contrast to the numerous reports dealing with the immediate results of ulcer treatment by the many antacids and other substances employed for this purpose, the papers in which the recurrence factor is stressed are not too many, and most of them are of relatively recent date. An impetus to the observation of the recurrence factor was given by the advent of products for the treatment of peptic ulcer, the supposed property of which was more the later increase of the resistance of the mucosa of the stomach and duodenum rather than

the immediate antacid effect. Obviously the effect of these substances could be observed only by long term experiments, using the length of the symptom-free period or lack of recurrence as a guide in therapeutic evaluation.

Some of the earlier reports dealing with therapy and recurrences of peptic ulcer came from the Lahey Clinic when Jordan and Kiefer (1932) (13) reported that in their private patients there was an incidence of 9% in one year, 19% in two years, and 46% of recurrences in five years. Emery and Monroe (1935) (14) observed 79% recurrences in one year and 93% in five years. Eusterman and Balfour (15) reported (1936) almost five year cures in about 50% of their ulcer patients, providing they were on a favorable environmental and therapeutic regime. Shortly thereafter St. John and Flood (16) reported among clinic patients a 68% recurrence rate within two years and 78% in five years. B. Crohn's (17) observation on recurrences of peptic ulcer is similar to that of St. John and Flood, while that of Bockus (18) comes closer to the observations of Eusterman and Balfour. Holland and Logan (19) observed in their private patients 65% recurrences in two years and 78% in five years, while Natvig et al (20) had 62% recurrences within three years in clinic patients. More recently, Rainondi et al (21) found an incidence of 66% of recurrences in the first year and 83% after two years. Hodges (22) reported on a small series of patients treated intensively in the hospital in 30% of whom recurrences appeared within one year. Flood (1948) (23) observed recurrences in 49% after one year and in 78% after five years. Smith and Jordan (24) found 20.1% recurrences in gastric ulcer

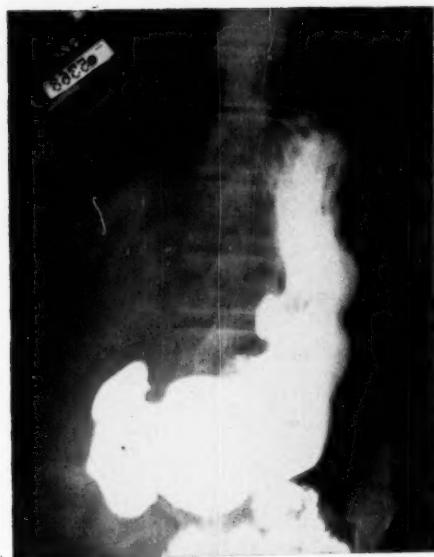


Fig. 3. Roentgenogram of gastric ulcer four weeks after medical treatment, indicating marked decrease in size of original crater.

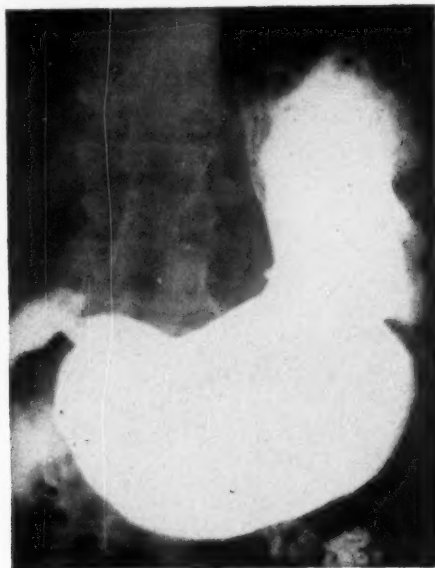


Fig. 4. Roentgenogram of gastric ulcer seen in Fig. 1 two months later, showing only small niche and beginning incisura opposite it.

patients after two years. Because of these frequent recurrences Holland and Logan believed that in gastric ulcer no recurrence within five years meant a cure, although in duodenal ulcers they had observed recurrences after ten and twenty years. The lack of recurrences has been observed particularly in the enterogastrone series reported by Ivy and associates (25).

Stimulated by the work of Ivy and associates with their mucosal "resistance raising" substance, an extract of intestinal mucosa, and the more recent findings of the importance of mucus as a preventive agent (26), some workers have reexamined the value of mucinous substances, particularly animal mucin, in the treatment of peptic ulcer. This reevaluation was made especially with mixtures of substances that were proved to produce an immediate symptomatic effect, such as the alkali and aluminum gels, and gastric mucin in various ratios—the latter as having both an immediate and late effect—i.e. increasing the resistance of the mucosa. Of the several such combinations offered in recent years to the clinician, a product combining aluminum hydroxide, magnesium trisilicate and gastric mucin seemed on observation to fulfill most of the criteria for a valuable antacid (including antacid and gastroscopic studies (27), (28)).

Because of the above observations, a clinical study using this new antacid was planned. The present paper deals with the results of this study, which has been extended for about two years (six months being the shortest period and two years the longest period of observation). It covers both the effect of this new antacid on the immediate symptoms and also on the rate and interval of recurrences.

#### MATERIAL

This series consists of 125 patients suffering from gastro-duodenal ulcer (17 gastric and 108 duodenal ulcers). The diagnosis was based on a careful history, routine physical examination, and roentgenological studies of the complete gastro-intestinal tract, including the gall bladder. The patients ranged from 26 to 73 years of age—50% of them were between 35 and 55 years of age. There were 18 women in the entire series. The patients in this series gave a history that ranged from three weeks to 40 years—the average being about eight years.

Seven patients had a history of perforated duodenal ulcer with closure of the perforation several years prior to this bout, and two had had previously gastro-enterostomies. Three patients had cholecystectomies previous to this attack. One patient with gastric ulcer had a thyroidectomy prior to admission. Eleven patients had pyloric obstruction with various degrees of gastric retention, ranging from 10% to 90% at the end of five hours.

Sixty-four patients in this series had previously been on antacids, such as Sippy powder, aluminum gels, magnesium trisilicate, calcium carbonate or gastric mucin; one had been on enterogastrone; and twelve had been on diet therapy alone. The remainder were on no particular regime.

The patients in this series have to be divided into two groups. The first group includes 105 patients and is composed of patients who were started on the new therapy because of an exacerbation or recurrence of symptoms during the period of this study. The second group consists of patients who were designated as

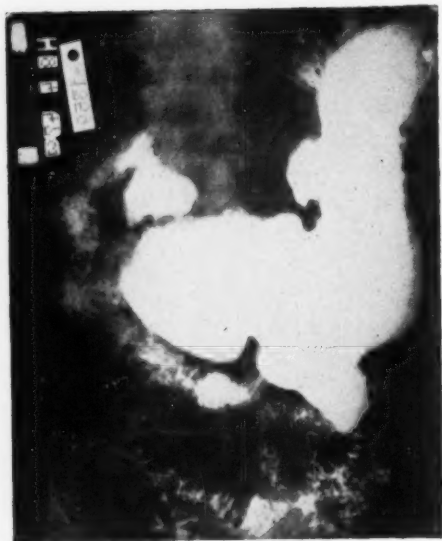


Fig. 5. Roentgenogram showing large irregular crater on lesser curvature pars media.

intractable cases, because they did not respond to an instituted medical regime until they were placed on the new therapy. Some of the patients in the latter group had been on alkali and various aluminum gel mixtures in addition to diet, sedatives and antispasmodics, but continued to have symptoms to such an extent that new therapeutic agents were indicated.

#### PROCEDURE

All patients were put on an ambulatory medical management, with the exception of six who were hospitalized. Of the latter, two had massive hemorrhages, one biliary dyskinesia with jaundice a sequel of a previous cholecystectomy, two had pyloric obstruction with 90% gastric retention, and one had acute alcoholic intoxication.

All patients were put on a bland diet, with milk and cream with meals and between meals. No night feedings were permitted. The majority of the patients were placed on two to four Mucotin\* tablets—one hour before meals, one hour after meals, and at bedtime. In those patients with severe symptoms, hourly doses of Mucotin were given. Night pain was controlled by Mucotin only. In some instances the patients were advised to set the alarm clock a half-hour to an hour prior to the time when the night pain usually occurred and advised to take two to four tablets. In every instance the patient was advised to chew and swallow the tablets without the aid of liquids. Antispasmodics and sedatives were given three times daily and at bedtime. Patients were advised against alcoholic beverages, coffee and smoking. Whenever indicated, psychiatric consultation was advised and utilized.

\*Aluminum hydroxide, magnesium trisilicate, mucin mixture tablet.



Fig. 6. Roentgenogram of gastric ulcer in Fig. 5 after two weeks of medical treatment, showing a smaller crater with smooth margins.

X-rays were taken before the start of the treatment and at various intervals during the therapy. The patients with gastric ulcer were x-rayed at weekly or bi-monthly intervals.

Gastroscopic examination was not done routinely in the duodenal ulcer group, but was done only when gastric pathology was suspected. In the gastric ulcer group, however, gastroscopic examination was routinely done and repeated at intervals of two to four weeks during treatment. Two patients were regastroscooped six months to two years after the ulcer had healed.

Thirty-two patients in the entire series were gastroscopied—17 of whom were gastric ulcers on x-ray and gastroscopic examination. The remaining 15 were diagnosed duodenal ulcer by x-ray, but because of suspected pathology were gastroscopied. Four of these 15 were found to have hypertrophic gastritis in addition to duodenal ulcer.

#### RESULTS

The results obtained with this new antacid were separated into two parts—the first part deals with the immediate effect on the presenting ulcer symptoms, and the second with the late effects or efficacy in controlling ulcer recurrences.

#### IMMEDIATE EFFECT:

The majority of the patients were relieved of their symptoms in the first seven to ten days of treatment. There were 12 patients in the group who did not respond to therapy, and food allergies were proven as a possible cause for their lack of response as demonstrated by routine skin tests, which in practically every instance were found to be positive to certain foods. The

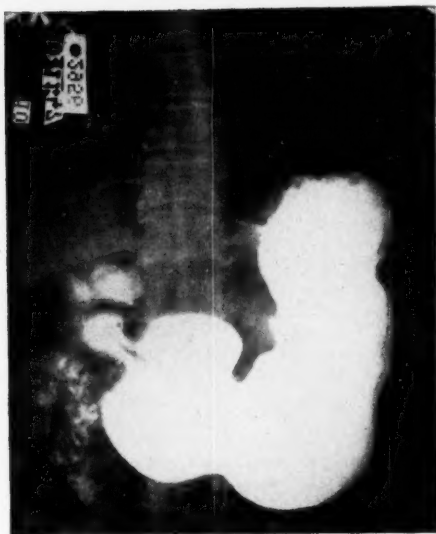


Fig. 7. Roentgenogram of stomach in Fig. 5 after eight weeks of medical treatment, showing only very small crater on the lesser curvature.

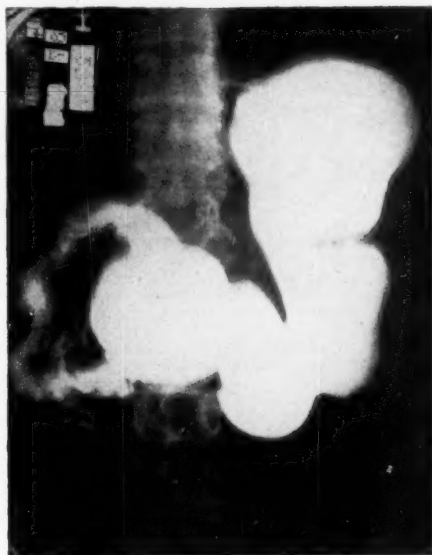


Fig. 8. Roentgenogram of same stomach one year later, showing a deep incisura on the greater curvature as the only sign of the previous gastric ulcer.

elimination of these foods and the administration of one of the anti-histamine preparations proved helpful.

Of interest here is the group of 20 cases with previously "intractable" ulcer symptoms despite an intensive medical regime—diet, sedatives, anti-spasmodics and antacids (alkali or aluminum gels)—which responded rapidly to the treatment with the new mixture of aluminum gels, magnesium trisilicate and gastric mucin. The response in these patients was only somewhat slower than in the ambulatory ones:

During the immediate management, one patient with a history of perforation and repeated recurrences received only partial relief on intensive medical therapy for eight weeks and was therefore recommended for gastroenterostomy and vagotomy; two had cholecystectomies for cholelithiasis and at the time of operation showed healed duodenal ulcers; and one was operated for hyperthyroidism during his treatment for gastric ulcer.

#### LATE EFFECT:

Eighty-nine patients had been on a treatment from 12 to 20 months; 28 patients from nine months to a year; and eight for less than nine months.

Of the 89 patients under treatment for more than one year, 53 had complete relief and to date have had no recurrences. Of the remainder, eight had slight to moderate recurrences following emotional upsets—one of these in addition to emotional upset also had a thrombosed hemorrhoid—four had partial relief; 12 admitted dietary indiscretion, which could account for their recurrence of symptoms—two of these had definite food allergies, and three had seasonal recur-

rences but of much milder form than previous to treatment; and in 12 patients the cooperation was poor.

Of the 28 patients under treatment from nine months to a year, 26 have had complete relief and no recurrence. The eight patients who had been under treatment for less than nine months all had prompt relief the first week and no recurrence to date.

Nineteen patients in the duodenal ulcer group were x-rayed six months to a year after treatment. Seven showed no deformity of the duodenum and 12 were assumed to be inactive by the roentgenologist.

Of the eleven patients with gastric retention (10% to 90% after five hours), nine returned to normal after a period of weeks, and two discontinued treatment.

In the 17 gastric ulcer patients, complete healing was observed clinically, roentgenologically and gastroscopically in every instance. Two patients in particular who were diagnosed carcinoma because of the size of their lesions, showed remarkable improvement clinically, radiologically and gastroscopically.

CASE 1: W.S., 47 years old, entered the hospital on April 6, 1948, stating that he was well until five months ago, when he began to have nausea and epigastric fullness after meals. Shortly thereafter he also noted that he was losing weight and was having anorexia and insomnia. About this time he began to experience sharp pain in the stomach, which would occur one hour or so after meals and which would be relieved by milk. There was no nausea, vomiting, hematemesis or melena. He was jittery and had lost 45-50 lbs. in the past five months.

His past and family history was irrelevant. He did not drink but smoked a package of cigarettes per day.

Physical examination revealed an emaciated white male, not acutely ill, but hiccupping. Blood pressure was 130/85, pulse 110 and irregular. Respiration and temperature were within normal. The right thyroid lobe was markedly en-



larged, but there was no displacement of the trachea. The lungs were clear. The heart was not enlarged, the tones were loud and irregular, a soft systolic murmur was present over the precordium. The abdomen was scaphoid but without tenderness and without palpable masses. Rectal examination was negative.

The initial diagnosis made was carcinoma of stomach, associated with either hyperthyroidism or carcinoma of thyroid.

The urine was negative; the Hb. 94%, RBC 4.30, WBC 14,400, with 86 polys, 10 lymphocytes and 4 monocytes. The Kahn was negative, B.M.R. was plus 24. The total protein was 6.2 gm. %, the cholesterol 107 mg. %, the NPN 30 mg. %. The EKG revealed auricular fibrillation. The stools showed + blood and his fasting free acid was 18\*. A Papanicolaou stain was negative.

The x-ray of the chest was negative. X-ray examination of the stomach April 23 revealed a very large crater along the lesser curvature in the upper third of the stomach (Fig. 1).

Gastroscopic examination April 27 was reported as follows: "An excellent view of the pylorus, antrum and angulus was obtained. On the anterior wall of the stomach toward the lesser curvature in the middle upper third of the stomach there was a huge crater with a yellowish-white base and surrounded by beefy-red edematous mucosa. Impression—large benign gastric ulcer."

The patient was put on a strict ulcer regime with Mucotin—two tablets every two hours—in addition to the antithyroidic regimen. He improved rapidly, gaining weight and being free of gastric symptoms. Repeat x-rays of the stomach, taken at weekly to bi-monthly intervals, showed a definite decrease in the size of the ulcer (Fig. 2 and 3).

Gastroscopic examination performed on May 14th and May 28th also were reported as showing continuous healing and decrease in size of the ulcer. On June 1st the patient was transferred to surgery for thyroidectomy. On June 11th patient had a thyroidectomy, from which he made an uneventful recovery. He left the hospital on July 2, 1948, without gastrointestinal symptoms and having gained 35 lbs.

The patient returned to the G. I. Clinic at periodic intervals and had repeated x-ray and gastroscopic examinations. There was a constant regression in the size of the ulcer (Fig. 4). When last seen (eight months later) there was only an incision noted opposite the place where the ulcer had been. Gastroscopically the ulcer crater had completely disappeared. The patient was completely free of symptoms on diet only.

CASE 2: E.L., a 60 year old Chinese, was admitted to the hospital complaining of pain in the stomach of a year's duration. This pain would occur particularly shortly after meals and would last for a while and be relieved by milk or medication. There was associated weakness and weight loss during the same period. No other history of significance was obtainable.

The physical examination revealed an elderly emaciated Chinese male, not acutely ill but showing signs of chronic illness. The only finding of significance was tenderness in the mid-epigastrium. A diagnosis of carcinoma of the stomach was made.

The urine was negative: Hb. 35%, RBC 2.07, and WBC 12,900. The x-ray of the stomach showed a large penetrating ulcer on the lesser curvature with 50% retention of Barium at the end of six hours. The diagnosis of malignancy of the stomach was made. (Fig. 5).

On gastroscopy August 15, 1947, the following observation was reported: "Large crater on the anterior wall and toward the lesser curvature. The crater is surrounded by a beefy red, swollen mucosa that gives one the impression of an angulus. The base of the ulcer is covered by a whitish-grey filmy coating." The gastroscopist considered the ulcer to be benign and suggested medical management under close observation.

The patient was put on a strict ulcer regime with two tablets of Mucotin every two hours as the antacid. The patient was re-examined roentgenologically and gastroscopically at frequent intervals and showed progressive healing of the ulcer (Fig. 6 and 7). Subjectively he improved remarkably well, gained weight and left the hospital completely well three months after admission. He returned at monthly intervals to the G. I. Clinic and when last re-

examined, in August 1948, there was no sign of the ulcer crater, neither roentgenologically (Fig. 8) or gastroscopically.

## DISCUSSION

The fundamentals of ulcer therapy have remained unchanged in the past 30 years. No medical management known thus far will permanently relieve ulcer symptoms\*, and the ultimate results of surgery for peptic ulcer are also not above criticism. The duty of the clinician is to institute the most suitable management for peptic ulcer with two results for his goal—one is to relieve the patient of his immediate symptoms, and the second is to prevent recurrences.

The relief and control of the immediate symptoms is usually not difficult in the majority of uncomplicated peptic ulcer cases. A program of more or less physical rest, relief from emotional tension, bland diet, antacids, sedatives and antispasmodics should benefit most of the patients complaining of symptoms due to a simple ulcer.

The prevention of recurrences of peptic ulcer is somewhat more difficult, since recurrences do not depend only on factors within the patient, but also on outside factors which tend to increase the stresses of the patient in one way or another. Worry, fatigue, anxiety, etc., may be more often the precipitating factors of a recurrence than dietary indiscretion, lack of taking the medication, or other deviation from the ulcer regime. Nevertheless an important factor in the prevention of ulcer recurrences is an adequate medical regime. Unfortunately "adequate medical regime" is interpreted variably by different men, and hence the statistics of recurrences may vary greatly. In general, an adequate peptic ulcer regime includes (1) a regularly eaten bland, gradually stepped up diet, which after three to six months becomes a general diet from which only certain "irritants or roughages" are excluded; (2) antacids, first at frequent—hourly to every two—intervals, and later only after and between meals; (3) antispasmodics; and (4) sedatives. Such a regime should continue with slight modification for six to twelve months. All too frequently, however, this regime is not adhered to as soon as the patient experiences relief of pain, and both the physician and the patient begin to compromise concerning diet, medication, etc. As pointed out by Althausen (29), such an adequate regime may lead to many cases of so-called "intractable ulcer" which are then subjected to unnecessary surgical intervention, and secondly, it may bring about "a state of pain relief in the presence of ulcer activity."

Besides the factors discussed above, other factors must be taken into consideration in a discussion of prevention of peptic ulcer recurrences. The patient must be educated to the ulcer problem, so that he neither magnifies nor minimizes the presenting symptoms. He must learn to recognize the influence of emotogenic factors, and the way every day problems in his business, home and society may affect the "sensations" in his abdomen. He must be educated to the variable influences that diet, stimulants (alcohol, coffee, condiments, smoking), various drugs, infections and seasonal changes may have on his ulcer symptoms,

\* (Note: Exception might be made for the possible prolonged effect of enterogastrone).



so that he might control them accordingly. The ulcer patient must also be taught to pay attention to minor exacerbations, because by promptly instituting treatment for mild symptoms he may prevent a full-blown recurrence.

If we accept the validity of Schwartz's dictum "no acid—no ulcer", a dictum which has been ably proven throughout the years by Palmer (30) and his associates, we must accept continuous neutralization or inhibition of gastric acidity as a paramount need in our attempt to prevent peptic ulcer recurrences. Our attention must, therefore, be directed towards a substance or substances that can fulfill the above need and thus protect the mucosa from ulceration. "Enterogastrone-concentrate" as prepared by Greengard, Atkinson, Grossman and Ivy (25) appears to date to be the only single substance to have protective properties in the experimental animal and has prevented recurrences in patients during observation of 12 to 28 months. The recent observation that gastric mucin injected intravenously into dogs suppressed gastric acidity (31) may explain some of the beneficial results reported previously with mucin therapy and more recently with mixtures of alkali and aluminum hydroxide containing gastric mucin (28). The latter type of medication may not only neutralize the excess acidity, but may also inhibit its secretion. Whether this inhibition is due to the mucin itself or to an enterogastrone-like substance in the mucin might be brought to light by some of the presently conducted tests on mucin (31).

In our study we were particularly impressed with the results of this new mucin containing antacid (Mucotin) in the small group of "intractable" ulcer patients

Thus patients who did not improve on medical regimes containing one or the other of several presently used antacids responded quite promptly when two tablets of Mucotin every two hours were substituted for the other used antacid. Furthermore, there seemed to be a more rapid rate of healing as noted from the prompt decrease in size of the observed gastric ulcers. This might have been due to the coating effect of Mucotin.

Mucotin, moreover, has also proven to be in general a good substance in preventing recurrences, although it must be stressed that our observation covers only nine to 24 months. Nevertheless it is significant that compared to other series of cases, the percentage of recurrences compares favorably with that of others. (Table I).

While the incidence of recurrences appeared somewhat lower in our series, there is a need for a definite determination of the causes for recurrences, because only thus can one assess the value of a therapeutic regimen. As pointed out above, recurrences may be due to a number of factors within and without the patients' means of prevention. Thus a review of the patients in our group who later developed recurrences disclosed several of the above enumerated factors as having been the precipitating agents in the recurrence of ulcer symptoms. In 24 patients poor cooperation as to diet and/or medication was the main cause for the recurrence. Of the remaining 14 patients who had recurrences, 13 presented various emotogenic factors as to the precipitating agents. In our "hindsight" opinion, adequate medical regimen in these 13 cases should have included additional psychiatric care if recurrences were to be prevented. In two of our patients, recurrences appeared

TABLE I  
REPORTS OF PERCENT (ADDITIVE) OF RECURRENCE OF PEPTIC ULCER SYMPTOMS AFTER VARIOUS LENGTHS OF OBSERVATION

	1 year	2 years	3 years	4 years	5 years	Remarks
Jordan & Kiefer	9	19			46	Private Patients
Emery & Monroe	79				93	
Balfour & Eusterman					50	Private Patients with Good Environ- ment Therapy
St. John & Flood		68			78	Clinic Patients
B. Crohn		About 68			78	
H. Bockus					About 50	
Holland & Logan		65			78	Private Patients
Natvig et al			62			Clinic Patients
Raimondi et al	66	83				
Hodges	30					
Flood	49				78	
Smith & Jordan		20				
Ivy et al	13	15	20			
Hardt & Steigmann	15*	18*				Clinic and Private Patients

\*If 24 patients who did not cooperate in the dietary and medical regimen were to be included, the percentage of recurrences would be 32 and 40 respectively.

simultaneously with an allergic food reaction. Such reactions are significant, because they may act as causative factors in a recurrence of peptic ulcer symptoms—a fact not too strongly stressed heretofore. Whether seasonal changes alone can be accused for the recurrences in the remaining three patients is a moot question. It is, however, of interest that only a small percent of the recurrences can be justifiably ascribed to the therapeutic regime using Mucotin as the antacid.

## SUMMARY

The clinical experiences in 125 patients, both as to immediate and late effect, with a new antacid "Mucotin" (aluminum hydroxide, magnesium trisilicate and gastric mucin mixture) are discussed in the light of recent ideas as to ulcer prevention and ulcer treatment.

This substance led to rapid clinical improvement during the stage of exacerbation and also apparently prolonged the pain-free intervals, having a recurrence rate of 15 to 18% in 12 to 24 months respectively.

Two case histories are presented as demonstrating the rapid healing in gastric ulcer.

The possible basis for the beneficial effect of this substance is discussed.

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# CHRONIC INTERMITTENT BENIGN DILATATION OF THE STOMACH

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IT IS well known that retention of the gastric contents for 24 hours or longer is usually indicative of an organic obstruction. Significant gastric retention of shorter duration, e.g., 6 to 12 hours—may be due to spasm of the pylorus secondary to inflammatory lesions or psychogenic stresses. In such conditions an x-ray of the upper gastro-intestinal tract reveals no significant passage of barium beyond the pylorus during the period of gastric retention. Retention occurring during acute dilatation of the stomach is accompanied by dramatic and alarming symptoms; there is active hypersecretion of the stomach, and the picture is one of urgency, requiring immediate and direct therapy.

The following is a report of two cases in which complete retention of the gastric contents was noted for more than twenty-four hours; and in which *no sign of obstruction or interference to the passage of the barium meal were found*. The symptoms, during the period of retention were minimal and exceedingly mild in nature. The x-ray picture was one of marked dilatation and atony of the stomach associated with a *patent and open pylorus, well-filled duodenum and normal jejunum*. (The last was easily demonstrated radiographically on moderate gastric compression).

The syndrome was noted in the course of two different gastric diseases and lasted 7 to 14 days after which the stomach spontaneously returned to normal. There was a tendency for the dilatation to recur intermittently.

## REPORT OF CASES

*Case I: Chronic intermittent benign dilatation of the stomach complicating gastric ulcer.*

W. H., a 40-year-old male, colored, was first admitted to the hospital on September 16, 1946. His history revealed periodic attacks of epigastric pain for 7 years prior to admission. These attacks would last four to five weeks, and were characterized by the appearance of epigastric pain 2 hours after meals, which was usually relieved by food. There was no history of night pain, nausea or vomiting. There were no tarry stools. The patient had intervals of freedom from pain between attacks, lasting 5 to 6 months. At time of admission, he had complained of symptoms for 20 days.

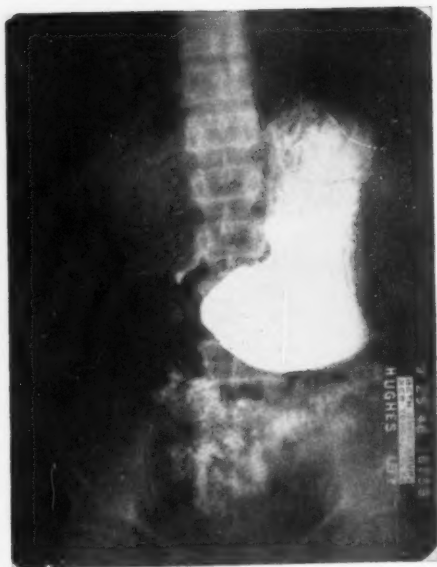
Gastro-intestinal x-rays revealed the stomach to be of normal size and tonicity with normal peristalsis. A small niche was noted on the lesser curvature 2" above the pylorus. There was no gastric retention after 6 hours. After 10 days of treatment, with a modified Sippy diet, antispasmodics and bed rest, he was discharged completely free of his symptoms. In March, 1947, patient was again admitted to the hospital because of recurrence of his pain, which had been present for two months. He described his symptoms as being similar to those noted in his previous attacks. In addition, he complained of a feeling of fullness and nausea, but no vomiting was noted. There was some fatigue and a slight weight loss. X-rays at this time revealed a completely different picture than that noted in 1946. The stomach was markedly dilated and weak peristaltic waves were noted. The ulcer niche on the lesser curvature was no longer visualized but a "flat line" was noted in

the same region. The pylorus was patent and wide open, the duodenal cap was filled with barium and the duodenum and jejunum were visualized without any evidence of dilatation or obstruction. There was no delay in duodenal or jejunal transit. Films taken 24 hours later revealed almost complete gastric retention. The stomach was still dilated and completely atonic. Physical examination at this time revealed a moderately distended, soft abdomen. No mass was palpable. Splash sounds were obtained on combined auscultation and percussion of the abdomen. The remainder of the physical examination and routine laboratory studies were within normal limits. Gastric analysis revealed normal "free" and total acid curves. Routine ulcer treatment, consisting of bed rest, bland soft diet, antacids and antispasmodics was instituted. Gastric aspiration followed by lavage with warm bicarbonate solution was done 6 hours after meals. One month after treatment no significant residue could be obtained on aspiration. At this time, x-ray examination revealed a stomach of normal size and shape in which good peristalsis and tonicity were observed. There was normal evacuation of the stomach contents and after 24 hours only a very small residue of barium remained. The patient was discharged asymptomatic shortly after. One year later the patient was admitted to the hospital with the same complaints. X-ray studies revealed the same picture of complete retention with a patent pylorus and duodenum. He was placed on a similar routine, and gastric aspiration and lavage were done daily until the stomach regained its tone. He was discharged symptom free after 4 weeks. The x-ray studies in this case revealed a marked dilatation of the stomach with a widely patent pylorus and no evidence of mechanical obstruction. One year later the patient was admitted to the hospital with the same complaints. X-ray studies revealed the same picture of complete retention with a patent pylorus and duodenum. He was placed on a similar routine, and gastric aspiration and lavage were done daily until the stomach regained its tone. He was discharged symptom free after 4 weeks.

*Case II: Chronic intermittent benign dilatation of the stomach complicating chronic inflammatory gastritis.*

D. D., a 41-year-old white female, was seen in July, 1932. History revealed the presence of acute epigastric pain of several weeks' duration without relation to food. The patient complained of frequent episodes of nausea which on 2 occasions were accompanied by vomiting. The history further revealed that she had complained of irregular mild post-prandial pain accompanied by nausea and constipation for several years. The present attack was the first in which the pain was acute and severe. Physical examination revealed a febrile emaciated white female. The abdomen was soft without evidence of peritoneal irritation, mass, or localized tenderness. The liver and spleen were not palpable. The rest of the physical examination was within normal limits. Barium x-ray at this time revealed a markedly dilated completely atonic stomach. A few weak peristaltic movements were noted. The pylorus was widely patent with good filling of the duodenal cap. Barium was visualized in the duodenum and jejunum and there was no evidence of dilatation or obstruction in these areas. There was no evidence of delay in transit from the duodenum to the jejunum. The stomach appeared to evacuate by the passage of very small amounts of barium, especially when compression was applied. A film 24 hours later revealed almost complete retention of the barium in the stomach. Repeated gastric analysis disclosed a complete achlorhydria. Gastric aspiration 12 hours after a meal showed a residual of 400 cc. Gastroscopy during the phase of dilatation showed the antral mucosa to be congested and somewhat thickened, but revealed no other change. The white blood count was 13,000. The smear showed a polymorphonuclear leukocytosis. Treatment at this time consisted of soft, bland diet, sedation, and the application of ice bags to the epigastrium. On this regimen, symptoms gradually disappeared and patient was

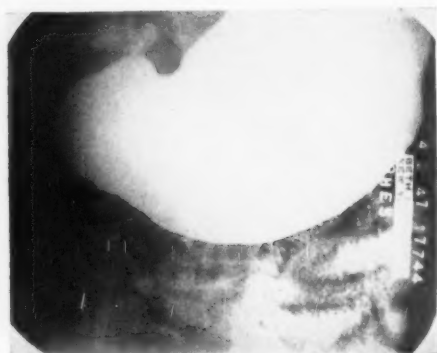
From the Medical Service of Beth David Hospital, New York, Dr. Louis Hauswirth, Director, and The Surgical Clinic of Salpetriere Hospital, Paris, France.



Case I: Films taken on 9/25/46 show a small niche on the lesser curvature of the stomach. No gastric retention or distension.



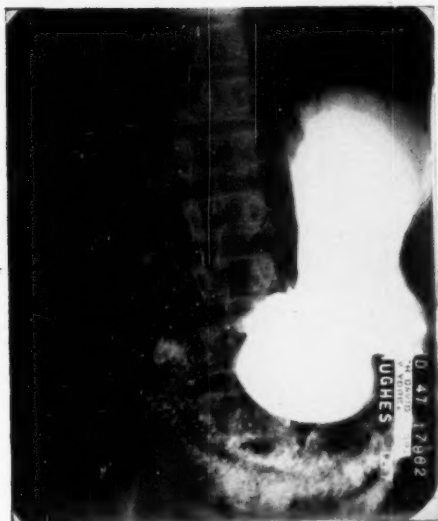
Case I: Films taken on 4/2/47. Considerable dilatation of the stomach. The pyloric canal is patent. Good filling of the duodenal cap. Small amounts of barium fill the jejunum.



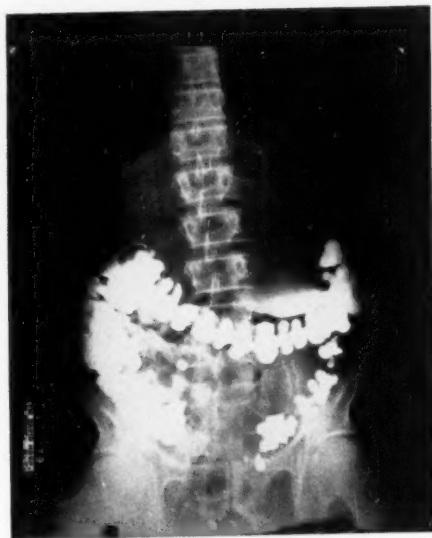
Case I: Film taken on 4/2/47—marked dilatation of stomach. The pyloroduodenal area shows filling with barium.



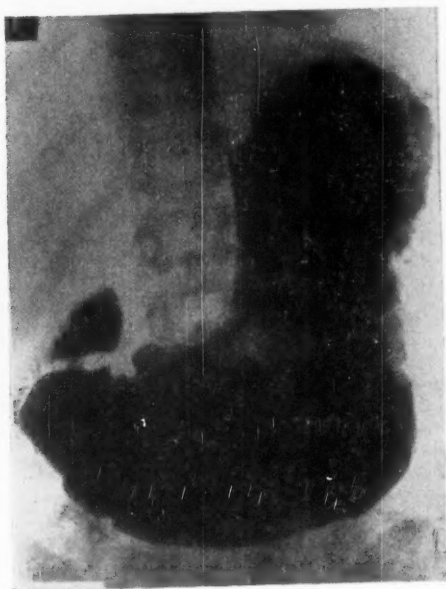
Case I: Films taken on 4/3/47—Almost complete 24 hour retention.



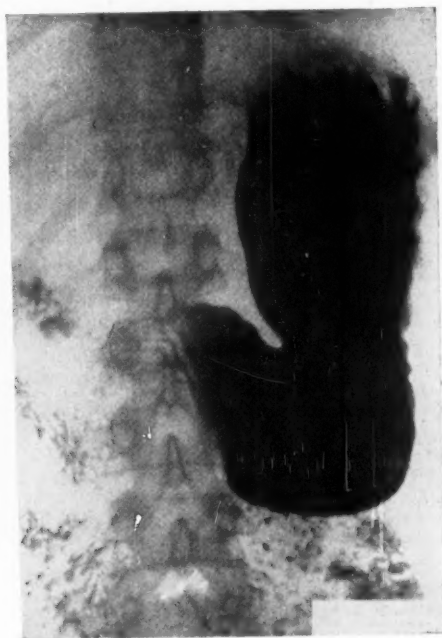
Case I: Film taken on 4/30/47, after treatment. The stomach has regained its normal size and tonicity. Good evacuation.



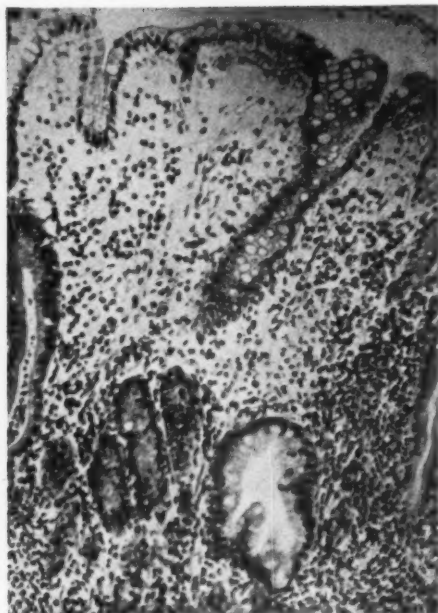
Case I: Film taken on 5/1/47. Slight 24 hour retention.



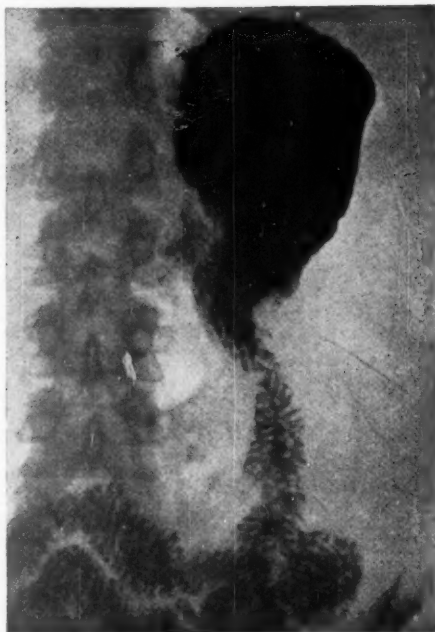
Case II: Film taken in August 1932. Very dilated stomach, with retention. Patent pylorus—good filling of the duodenal cap.



Case II—Films taken in October 1932, during a "free interval." The stomach has regained its normal size, normal tonicity and evacuation.



Case II—Surgical specimen showing marked inflammatory reaction and edema of mucosa.



Case II: After gastrectomy. Good tonicity is noted in gastrectomized stomach.

symptom free by October 15th. In November, 1932, an exploratory laparotomy was performed. The stomach was entirely within normal limits, except for the presence of enlarged lymphnodes along the lesser curvature. The abdomen was closed without surgical intervention, and the post-operative course was uneventful. Following recovery, gastro-intestinal x-rays were repeated. The stomach appeared entirely normal with good tone and peristalsis. There was no evidence of dilatation or retention, and no gastric residue after 24 hours. A gastroscopic examination at this time was within normal limits. In the months following, the patient continued to have repeated attacks identical to that complained of on admission. These appeared to be self limited, and the stomach returned to normal between episodes. Because of the recurrence of the syndrome, with associated fever and leukocytosis, a tentative diagnosis of chronic inflammatory gastritis was made. A sub-total gastrectomy was performed during an asymptomatic period. The gross appearance of the gastric mucosa was normal. However, histological examination revealed a marked infiltration of polymorphonuclear cells, extending through the mucosa without involving any other layers. The picture was that of a chronic inflammatory gastritis. Careful aerobic and anaerobic cultures done immediately after the removal of the specimen resulted in a growth of streptococcus viridans from the mucosa. The patient had an uneventful post operative course and has had no recurrence since her operation. The x-ray studies clearly demonstrated the existence of a dilated stomach with a widely patent pylorus on several different occasions.

#### COMMENT

It is of interest to speculate as to the mechanism of prolonged retention in the face of a patent pylorus and duodenum.

According to the classical explanation of gastric emptying, large peristaltic waves (prepyloric in type)

so increase the pressure in the antrum that the pyloric sphincter is forced open and gastric contents pass through. If one takes into consideration the fact that the peristaltic wave never approximates the walls of the stomach it is difficult to see how any significant pressure can be built up in the gastric segment distal to the peristaltic wave. Any increase in pressure would tend to equalize itself throughout the entire stomach, and since the portion of the viscus proximal to the wave is in a state of comparative relaxation, it would seem that any increase in pressure would be equalized by a dilatation of that portion of the stomach. The fact that peristalsis was present in the reported cases and that, in spite of a patent gastric exit, no significant emptying could be demonstrated, tends to substantiate the criticism of the role of peristalsis in gastric emptying.

More recently (1, 2) it has been postulated that the "tonicity" of the whole gastric wall is the important factor in the emptying of the stomach. The "systolic" contractions of the whole wall creates an increasing pressure gradient throughout the stomach which is followed by a relaxation phase and by this mechanism contents are ejected through the pyloric canal when the gradient of pressure attains sufficient force.

If one accepts the latter point of view, then a decrease in the tonicity of the gastric wall and a weakness of the muscular contraction during the systolic phase could explain the marked retention reported, despite the presence of peristalsis and the patent pylorus.

Why this transient paralytic state should occur is



somewhat obscure at this time. Insofar as the second case is concerned the invocation of Stokes Law which states that the muscularis beneath an inflamed mucosa is temporarily paralyzed may be of help in an attempt to explain the phenomenon. (3, 4). Certainly the necessary condition can be presumed to have been present in the second case. In the first case, in which a gastric ulcer was the fundamental abnormality, the concomitant gastritis may possibly have played a part, but benign dilatation is not a common complication of ulcer, whereas an associated gastritis is, so that much emphasis can not be placed on this mechanism.

Chronic intermittent benign dilatation of the stomach may be considered a complication of peptic ulcer and other gastric disorders. It is certainly not to be considered an indication for surgery. In view of its minimal symptomatology and good prognosis, surgery during the phase of dilatation is contraindicated. Resection would result in an inordinately high stoma when tonus is regained. The edematous tissue of the distended stomach would make for poor suturing and slow healing. If surgery is necessary for other reasons, it would be better to wait until the benign dilatation has been relieved by medical measures, prior to operating. This was done in the second reported case with good result. It is interesting to note that surgery in this instance was resorted to because of recurrent inflammatory disease which, in all probability, would have responded to proper antibiotic therapy had it been available at the time.

#### SUMMARY

1. Two cases of chronic intermittent benign dilatation of the stomach are reported. This syndrome is

characterized by a) complete gastric retention for at least 24 hours without evidence of obstruction at the pylorus or in the duodenum or jejunum, b) extremely mild symptoms, c) rapidity of onset with a duration of 7 to 14 days followed by spontaneous remission and d) a tendency to recur. The cases reported describe its occurrence during the evolution of a gastric ulcer and as a complication of infectious gastritis. In the second instance, histological examination of the surgically removed stomach failed to reveal any morphological abnormality of the muscularis of the stomach or pyloric sphincter.

2. The radiological examination revealed a markedly dilated and atonic stomach, with a patent pylorus and a well filled duodenal cap. Peristalsis was present but slightly diminished. These observations suggest that failure of the stomach to empty itself is due to the impairment of "pump action" and tend to support the theory that "pump action" is the responsible factor in gastric emptying.

3. The nosological place of the syndrome and therapeutic implications are discussed.

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## RESISTANT BACILLUS FRIEDLANDER PYELITIS IN DIABETES MELLITUS: RECOVERY WITH AUREOMYCIN THERAPY

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A COMMON precipitant of diabetic acidosis is a genitourinary infection. Unfortunately the symptoms relating to that system may be overlooked as a part of the general condition until too late. At the Philadelphia General Hospital approximately twenty percent of the cases of diabetes mellitus seen at postmortem examination have genitourinary tract infections, with the ascending type of pyelitis being more frequent than the hematogenous source. A conservative estimate would indicate that this complication is the immediate cause of death in one-third of the cases with genitourinary tract infection. *Bacillus coli* is by all odds the chief offender. However, the frequency of *Bacillus Friedlander* pyelitis in the diabetic service is a fact that needs to be stressed, especially in view of some of the growth characteristics. The organism appears to

be resistant to the usual antiseptics and antibiotics, especially in diabetic individuals and perhaps it is on the increase because of that.

The studies of Root (1) reveal similar findings although he found the hematogenous source was responsible in fifty-five percent of the cases along with positive blood cultures in two-thirds of them. The question might be raised here whether or not the septicemia was of renal origin. Friedlander's infection is not a rarity and constitutes about one percent of the admissions to the metabolic service at the Philadelphia General Hospital.

The part that neuropathy plays in predisposing patients to pyelitis needs more investigation. It seems quite evident that sphincter disturbances and those of sensation which could contribute to an atonic and/or dilated bladder are common. Rundles (2) felt that thirty percent of diabetic neuropathics show evidence of disturbance either subjectively or objectively of the genitourinary tract. So achalasia of the detrusor and external sphincter constitutes a definite hazard.

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Greene (3) has pointed out that the behavior of the insulin requirement in infection is not entirely uniform or predictable; yet, it would seem safe to assume that generally in upper urinary tract infections the insulin requirements rise considerably and regular insulin must be employed in the therapeutic attack.

Finally, is there less resistance to infections in the diabetic state per se, or is it only because of inadequate control? There is evidence (4) to suggest that the most reliable index as far as antibody response goes is the state of nitrogen balance. For when the patient is controlled by diet and insulin, the antibody response to typhoid antigen is within normal range provided the serum proteins were adequate.

#### CASE REPORT

N. C. was a 44-year-old white male of Italian descent who was admitted the first time to the Philadelphia General Hospital on 8/11/47 complaining of weakness and weight loss. He was found to have diabetic acidosis. Also there was a urethral stricture that responded nicely to dilatation. (At that time he received a course of urotopin and his blood urea nitrogen was 21 mgs. percent. Cardiac and ophthalmologic consultations were essentially negative.) He was discharged 9/20/47 on a diet 90 P 110F 220C, and 25 units regular insulin with 20 units protamine insulin before breakfast and 12 units regular insulin before supper.

He was readmitted 11/20/47 with similar complaints and his blood urea nitrogen was found to be 25 mgs. percent. Intravenous urogram studies revealed bilateral hydronephrosis and hydroureters. This was more marked on the right. *Bacillus coli* was found on urine culture and the patient was placed on sulfadiazine one gram four times a day. Catheter drainage was instituted at once prior to a transurethral resection. The patient improved and discharged himself without the physicians' consent 1/10/48.

On 3/1/48 he returned again and was admitted from the receiving ward as a toxic psychosis. At this time he was found to have latent lues. The offending system was still the genitourinary tract and the organisms isolated on culture were *bacillus coli* and *bacillus pyocyaneus*. His blood pressure was 125/65, pulse 70 and regular. The blood urea nitrogen was 25 mgs. percent. He was placed on catheter drainage again and given a course of the combined sulfadiazine-sulfamerazine therapy, one gram of each four times a day. The insulin requirements did not rise appreciably at this time and the urine became clear in a short period of time. He was discharged 4/22/48 improved.

Finally he was admitted on 10/9/48 in a comatose state and having clonic convulsions of the upper part of his body. His body was poorly developed and nourished. His head and eyes turned to the left. He was dehydrated, warm and there was no evidence of trauma. The temperature was 99°F., pulse 120, respirations 16, and the blood pressure was 125/65. Examination of the eyes showed dilated pupils that did not react to light. The conjunctivae and sclerae were normal in appearance. The oral cavity was in a poor hygienic state with various teeth and numerous extractions. Eye grounds revealed no abnormality. There was some stiffness of the neck and discrete non-tender posterior cervical adenopathy. The thyroid gland could not be palpated. The thorax was asymmetrical with a Harrison groove on the left. In addition, there was some atrophy of chest muscles on the left with limited expansion. The lungs were clear and the heart was not enlarged. There was a simple tachycardia but no murmurs were heard. The liver edge could be palpated two fingers breadth below the costal margin. It was slightly tender and smooth. Normal peristalsis was present and slight costovertebral tenderness could be elicited. The extremities and genitalia were negative. Neurological examination showed weakness of the entire right arm but no definite complete paralysis. Reflexes were hyperactive but no abnormal ones were elicited. The patient was unresponsive except to pain stimuli. Trousseau's sign as well as Chvostek's sign was negative. The patient experienced tonic and clonic convulsions every three to five minutes for several hours after admission despite active therapy.

Laboratory studies on admission were hemoglobin 13.1

Gm.; leucocyte count 12,000 with 89 percent polymorphonuclear cells. Blood sugar determination was 746 mgms. percent. Carbon dioxide combining power was 36 volumes percent and the blood urea nitrogen was 60 mgms percent. The total calcium in the serum was 11.1 mgms. percent and the phosphorus was 3.3 mgms. percent. Later when the serum protein determination was completed, i. e. total 7.8 Gms., with albumen 5.6 Gms. and globulin 2.2 Gms., the ionized calcium was found to be within the normal range. Urinalysis revealed specific gravity 1014, trace of albumen, four plus sugar and .30 leucocytes per high powered field. Later urine culture yielded *bacillus pyocyaneus* and *bacillus Friedlander*.

The patient responded nicely to hydration, insulin and tidal irrigations with a quarter percent phosphoric acid solution. So a chest x-ray was taken the next day. This revealed calcification of the pleura on the left side, slight elevation and some adhesions at the base of the left diaphragm. There was a normal cardiothoracic ratio and the chest was otherwise clear. Electrocardiogram showed a normal tracing with slight left axis deviation. Because of the persistent neurological symptoms a spinal puncture was performed. The pressure was normal and no cells were seen. The spinal fluid protein was 39 mgms. percent and the Wassermann reaction was negative. The blood Wassermann reaction was positive and there was a quantitative Kahn titer of 69 units. Skull x-ray was negative.

The results of the therapy and the type can best be shown in the following table with representative values selected. The impression on admission was: Diabetes mellitus with acidosis, pyelonephritis and bilateral hydronephrosis, urethral stricture, encephalopathy on an azotemic basis.

TABLE 1

Height 5'6" Weight 152 lbs. Diet 90P 110F 220C		Patient N. C. Total Fluid Average 3000		N. C. cc/daily Insulin/ daily	
Date	Blood Sugar mgm/%	Blood Urea Ni- trogen mgm/%	CO <sub>2</sub> Combining Power Vol/%	Regular	
10/9/48	750	60	36	65	
10/10/48	652	48	33	65	
10/11/48	241		39	35** 0-20	
10/16/48	468	35	32	35 10-30	
10/21/48	262 362*			50-15-50	
10/24/48	780	33		70-25-50-20	
10/27/48	135 410*	54	38	90-45-85-15	
10/30/48	110 330			110-40-70-20	
11/4/48	95	51		100-25-30	
11/7/48				80 10-20	
11/12/48	116			40 0-0	
11/16/48	168 337	40		40 0-0	
11/28/48	124			55 0-0	
12/10/48	139 113	51		55 0-0	
12/24/48	124	24	41	50 0-10	
1/2/49	198			30 0-0	
1/10/49	150 100	26		30 0-0	
1/30/49	110	24		20 0-0	

\*Two hour post prandial sugar.

\*\*Ante cibum 3 x day.

The patient was started on penicillin empirically on admission 10/9/48 in a dosage of 50,000 units every three hours. This seemed to improve the clinical well-being of the patient, but it was discontinued 10/15/48 when the urinary tract organisms were still present unchanged. One will recall the patient had previously received the ordinary urinary antiseptics. Since the main offender appeared to be *bacillus Friedlander* which could not be typed, streptomycin therapy was begun 10/16/48 with a dosage of a half gram twice a day. This was continued until 10/27/48 while sensitivity tests were being done. In the meantime the serum was checked for antibodies and a titer of 1/40 dilution agglutinins was demonstrated against that particular strain. Blood cultures were negative. This relatively high value would seem to imply good host resistance and with an unabated clinical picture a resistant organism. The sensitivity tests revealed that this particular strain required more than 40 units per

cubic centimeter to inhibit growth, and in a like manner was resistant to sulfadiazine. It did not seem feasible to attempt to get that high a level in man so the drug was discontinued.

Now the blood urea nitrogen remained high though there was a normal creatinine value of 2.4 mgms. percent. Phenolsulfonphthalein tests gave values less than 10 percent. for two hours and the urea clearance value was around 5 percent. However, since tissue concentration and not plasma or urine levels per se seems to be the important criterion, the sensitivity to other antibiotics was carried out. It was demonstrated that the organism *Bacillus Friedlander*, type unknown, was sensitive to less than one microgram per cubic centimeter of polymyxin, aerosporin, bacitracin and aureomycin. Since the former are somewhat impure and with bacitracin having some nephrotoxic action, it was decided to try aureomycin at once.

On 11/2/48 aureomycin (5) in a dosage 20 mgms. every six hours was begun. As shown in the preceding table the insulin requirements were at their height, roughly 240 units regular insulin per day, and within forty-eight hours there was a drop of a hundred units. Persistently positive urine cultures taken every third day were obtained up to the time aureomycin was begun. On 11/10/48 the first negative urine culture was obtained although *Bacillus pyocyaneus* was still present. The aureomycin had to be discontinued as the supply had run out on 11/9/48. The *Bacillus pyocyaneus* later disappeared and all subsequent urine cultures were sterile. The insulin requirements dropped to 40 units regular insulin daily by 11/12/48 and the blood urea fell gradually to 24 mgms. percent. (\*A repeat was obtained on the serum agglutinins.)

The patient was operated upon 12/31/48 under spinal anesthesia, the diagnosis being contracture of the vesical neck and prostatic hypertrophy grade 1. About ten grams of tissue was resected and the patient made an uneventful recovery. He was discharged 1/11/49 on a diet 90P, 110F, 220C with 20 units regular insulin before breakfast daily. His post-operative blood urea nitrogen was 26 mgms. percent and a phenolsulfonphthalein test showed 30 percent in two hours. A urea clearance test gave a value of 80 percent average normal. When seen after a month's interval he presented a cheery disposition and appeared quite healthy.

#### DISCUSSION

This report will serve to renew interest in the mechanism of insulin resistance in infection. Here the word "resistance" is used to denote a daily requirement over 40 units regular insulin since total pancreatectomy has verified this amount. Insulin resistance studies customarily run through a gamut as (1) impotency, (2) delayed absorption, (3) other endocrine disorders, i.e. pituitary, thyroid, adrenal and ovary; (4) liver function, (5) allergy, (6) infection, (7) pancreatic function, (8) psyche, (9) muscle glycogen mobilization.

In infection there are increased metabolic requirements and hence a relative lowering of endogenous insulin. There may be a toxic factor in addition from the breakdown of tissues, i.e. leucocytes that may act on the islets, possibly to stimulate the alpha cell secretion and/or depress beta cell function. The alarm reaction, with its outpouring of 11 oxysteroids (6) and adrenalin may throw a severe burden on an inadequate pancreas especially if in infection muscle glycogen is mobilized almost as readily as liver glycogen. The kidney can form glucose, and maximum resorption by the tubules of glucose has been shown to take place at high levels, around 350 mgms percent. There is usually stasis present in genitourinary tract infections and, in addition, if the patient is a diabetic, the renal factor increases in importance.

Recently the importance of the ubiquitous "Gluta-

\*The test for serum agglutinins was repeated in December and a titer of 1/20 was demonstrated.

thione" was re-emphasized. When the level in tissues or plasma falls, more insulin is needed. This enzyme probably keeps the sulphydryl groups in insulin active.

As to the importance of neuropathy on bladder function Campos (7) found that over 90 percent had a higher than average normal capacity as demonstrated by cystometric measurements on 26 unselected cases. Two-thirds were definitely pathologic although only 6 gave values concordant with atony of the neurogenic type. Experience with a few cases at the Philadelphia General Hospital is in accord. Hence after evaluation by urinalysis, culture, I. V. urogram and cystoscopy, a parasympathomimetic drug may be employed with beneficial results.

Why did aureomycin work when streptomycin did not? It appears to be a matter of pH since the diguanidino groups on the streptomycin compound make it very susceptible to shifts toward the acid side. In fact (8) resistance to the drug increases out of proportion to the lowering of the pH. One would think the two antibiotics would be equally effective if gram negative organisms (9) are supposed to synthesize all their essential amino acids from ammonia and carbon dioxide. It may be well to give some idea of the plasma and urine levels on the prescribed dosage, 20 mgms. every six hours. The plasma level at one hour was .2 microgram per cubic centimeter, and at three hours was less than .1 microgram per cubic centimeter. The urine levels were around twenty micrograms per cubic centimeter at three hours. It would seem that the sensitivity levels and bacteriostatic levels have rather wide variables but generally go in the same direction.

According to Ayrazian (10) the incidence of diabetes in Friedlander infections reported in the literature is roughly 20 percent. Since the virulence of the organism is conditioned by the amount of capsule formation and since it has been demonstrated that media with .3 percent glucose promotes the maximum growth of capsule, it may be that this accounts for the increased frequency of Friedlander infections in diabetics.

In the handling of genitourinary tract infections it is best to wait with the patient on continuous catheter drainage until the blood urea nitrogen has stabilized before surgery is performed. The neuropathy will disappear only after prolonged control of the diabetes and it may be advisable to increase the diet considerably even though the insulin consumption goes up along with it. Parasympathomimetic drugs can be employed to good advantage in the interim.

#### CONCLUSION

This case presents a multitude of problems inherent in the management of genitourinary tract infections in the moderately severe diabetic patient. Many questions are posed along with a brief background for them. In summary, (1) aureomycin was found to be most effective in the treatment of *Bacillus Friedlander* pyelitis; (2) the diabetic state may enhance the virulence of the organism; (3) neuropathy, especially involving the nervi erigentes may predispose to genitourinary tract infections; (4) transurethral resection was very effective despite the neuropathy.

The author is indebted to Dr. Harold Zintel of the University of Pennsylvania Hospital for the supply of aureomycin (Lederle) and the bacteriological reports presented, and to Dr. Edward S. Dillon for his helpful criticism.

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## ANEURYSM OF THE COMMON ILIAC ARTERY REVEALED BY PROCTOSCOPIC EXAMINATION (CASE REPORT)

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**A** CASE of dissecting aneurysm of the right common iliac artery is presented because similar cases are rare, the lesion, in this instance, produced urinary obstruction and signs of impending large bowel obstruction, and a presumptive diagnosis was made by both digital and proctosigmoidoscopic examination.

That the lesion is rare is substantiated by Brewer, (1) who in 1941 reported a case of dissecting aneurysm of the common iliac artery and stated that but three similar cases had been reported previously.

According to Bell, (2) a dissecting aneurysm is a lesion in which the blood enters a tear in the media, so that the vessel is composed of an inner tube consisting of intima and inner media, and an outer tube consisting of adventitia and outer media. The arterial wall shows ectasia and medial degeneration. The tear usually runs transversely. The lesion occurs chiefly in persons over 50 years of age. Arteriosclerosis and infection are usually responsible.

Among the extra-rectal masses which may be detected by thorough proctosigmoidoscopic examination are the following: Prostatic abscesses and tumors, enlargement of the seminal vesicles, Blumer's shelf, pelvic tumors, sacro-coccygeal tumors and cysts, ropelike loops of bowel as seen in cases of ileitis, fecaliths in proximal loops of bowel and aneurysms. The case to be presented belongs in the last group. The presence of aneurysm is suspected when a pulsating extra-rectal mass is evident.

Aneurysms of the iliac arteries produce urinary symptoms. Taylor, (3) in 1939, had a case in which the lesion had ruptured into the ureter. The finding was verified by autopsy. Lazarus (4) in 1944 discussed the effect of this type of lesion on the urinary tract under the following classification: (1) changes in local circulation, (2) changes due to interference with renal drainage, (3) changes due to direct pressure on the kidney.

More recently, Dillon and Torassa (5) published a

paper on aneurysms involving the urinary tract. Three cases were presented, one in which the aneurysm involved the kidney, the other two in which the lesion involved the common iliac artery. The latter two cases were managed successfully by surgery. Goodwin and Shumacher (6) presented a similar case.

Whiteside (7) has reviewed effectively the surgical anatomy of the left common iliac artery. Branches of the presacral (sympathetic nerve) and parasympathetic nerves, left ureter and superior hemorrhoidal artery are anterior to the left common iliac artery. The fourth lumbar sympathetic ganglion, lumbosacral nerve trunk (L. 4 & 5), the obturator nerve, ilio-lumbar artery (from the posterior branch of the hypogastric-internal iliac) the sympathetic chain and common iliac lymph-gland lie posterior to the left common iliac artery. The psoas muscle is lateral as well as the genito-femoral nerve. The common iliac vein is medial to the left common iliac artery. In the event of blockage of the common iliac, the following anastomotic vessels would function: (1) Inferior mesenteric above with anastomotic branches of the hypogastric below; (2) Ovarian or spermatic with uterine or vesical arteries; (3) Middle sacral above with lateral sacral branches of the hypogastric below.

After consideration of the anatomy described by Whiteside, it is easy to understand the pathologic changes resulting from a dilatation of the common iliac as occurs in aneurysmal change. These changes could conceivably include urinary obstruction, vascular occlusion and pressure on nerves resulting in various neurological disturbances.

### CASE REPORT

The patient, Mr. A. O. White, age 67, was admitted to the Allentown Hospital on August 15, 1947. He presented the chief complaint of pain at the coccyx and inability to empty his bladder. His present illness began about August 1946 with pain at his coccyx, especially when sitting, and numbness of the right great toe. During a period of several months he developed pain over the entire right leg with numbness over the lateral portion of this leg. In March 1947, he developed a "cold" characterized by chills and fever. During the past six months he had increased difficulty in voiding and on admission was unable to void. He gave no history of hematuria. He used laxatives regularly for several years.

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Systemic history provided no additional information. Family history indicated no evidence of cancer, tuberculosis or diabetes.

Physical examination revealed a well-nourished white male. Head and neck appeared normal. The lungs were clear to auscultation and percussion. The heart appeared to be of normal size. There was a loud blowing systolic murmur over the entire precordium but heard best at the apex. Pulse 72, blood pressure 120/80. The abdomen was slightly distended. Percussion indicated bladder was distended to 2 centimeters below the umbilicus. A deep pulsation was palpated beneath the bladder and particularly to the right side. The femoral artery on the right was more prominent than the one on the left. The extremities appeared normal to inspection. The external genitalia revealed no abnormalities. Proctosigmoidoscopic examination for a distance of 24 centimeters revealed normal mucosa. However, a large smooth firm pulsating tumor was discernible anterior to the rectum. The prostate appeared normal. The lower border of the tumor appeared to be just above the prostate and extended on either side of the

entire course. The right kidney revealed hydronephrosis and its ureter was distended. There was a mass, 5 centimeters in diameter, in the right lower abdomen, beneath the peritoneum, which proved to be a dissecting aneurysm of the right common iliac artery (Fig. 1 & 2). Microscopic section, subsequently, revealed degeneration of the media and thickening of the intima. A section of the abdominal aorta showed arteriosclerotic changes. The bladder appeared normal except for hyperemia of the mucosa.

Immediate cause of death was not established. Autopsy did not include examination of the brain and for this reason, cerebral hemorrhage could not be excluded.

#### SUMMARY

A case of dissecting aneurysm involving the right common iliac artery is presented. It represents a comparatively rare lesion, and in this instance, the presumptive diagnosis was made by proctosigmoidoscopic

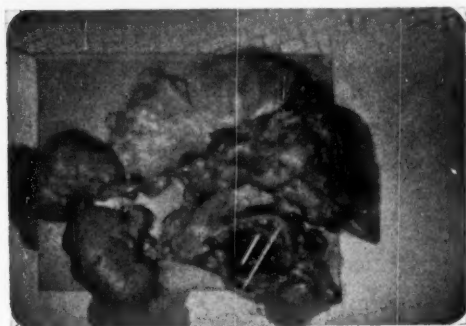


Fig. 1. Shows aneurysm after it has been opened. Kidneys, dilated ureters and sigmoid colon are demonstrated.

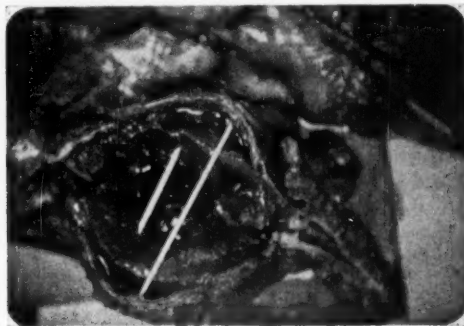


Fig. 2. Detailed picture of dissecting nature of aneurysm.

midline, but was more prominent on the right. It was impossible to estimate the size of the tumor, although it was at least as large as an orange.

Complete blood count and urine were within normal range. Wassermann reported negative. Urine showed light cloud of albumen, 100 white blood cells and 25 red cells per high powered field. Electrocardiogram revealed normal findings. X-rays of chest and abdomen were insignificant. Intravenous urogram revealed hydronephrosis and hydro-ureter on the right. Cystoscopic examination revealed normal prostate, elevation of the floor of the bladder on the right from extrinsic pressure and obstruction at the right ureterovesicle junction.

The patient did not improve. He suffered intermittently from chills and fever. Temperature frequently as high as 104°. Marked abdominal distention was noted on August 28. Rectal examination on August 29 revealed patulous anus and the tumor appeared to have become distinctly larger. In spite of supportive and antibiotic treatment, the patient died on August 30.

Autopsy was performed. The lungs and heart showed no significant findings. The stomach, liver, gall bladder and small bowel appeared normal. The entire large bowel was moderately distended. The left kidney was of normal contour and size, but its ureter was dilated throughout its

examination. The lesion was far advanced when discovered and had already produced urinary obstruction with a fatal termination. Autopsy verified the diagnosis.

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## NUTRITION NOTES

### THE NUTRITION OF TEETH

The problem of dental health, apart from the restorative efforts of dentists, seems equally if not more involved than the health of many other organs. Methods of dental repair have reached a zenith of perfection due to the efforts of an alert American dental profession, yet it is true that there is nothing that such repair can do to prevent further caries. Shaw (1) has recently pointed out that dental personnel in this country are incapable of taking care of more than one quarter of the actual need for dental treatment.

Careful dietary selection holds considerable promise for preventing tooth decay. Liberal amounts of milk, cream, butter, eggs, meats, vegetables, fruits, cereals and cod-liver oil appear to be effective for growing children, although not effective in every case. The environment of the tooth is granted importance, but many of the diets effective against dental caries have not been low in carbohydrates. A survey of over 750,000 children in Europe during the past 40 years showed that toward the end of both world wars, there was a substantial reduction in dental decay. While the sudden reduction of carbohydrates during rationing produced an alteration in oral environment within a period of two years following the inception of rationing, it was not until six or seven years had passed that the lowered incidence of dental caries was noted. The teeth most benefited by wartime conditions were those which began to develop after rationing was established. It appears that we may expect more results in the reduction of dental caries from dietary control than

any other method, but it is still impossible to list nutrients responsible for such influences, or even to name the foods which contain them.

(1) Shaw, J. H.: Nutrition and dental caries. *Nutrition News* 13, 341.

### U. S. FOOD SUPPLY

The consumer price index of retail foods in the United States reached its highest point of 174 in the summer of 1948. (The prevailing prices from 1935-39 are taken as 100). The year 1948 ended at 168. The consumption of food per capita of civilian population in 1950 is expected slightly to exceed that of 1949 with some further decline in food prices. Citrus fruits will be scarcer because of reduced supplies of fresh grapefruit. More frozen orange juice will be available on the market. The increased consumption of pork, turkey, potatoes, leafy, green and yellow vegetables, and sugar, will result in a halt in the downward trend since 1946 in the supply of most nutrients. It will also result in a one to two per cent increase in available food energy, fat, vitamin A, thiamine and niacin. The loss of ascorbic acid due to frost damage and tropical storms may be made up by increased use of tomatoes and leafy, green and yellow vegetables. The loss in protein due to decline in milk consumption may be offset by increased egg consumption. Of major significance is the reduction in available supplies of calcium resulting from the continued decline in the use of fluid milk and cream. (The National Food Situation, Jan-Mar. 1950. U. S. Dept. Agriculture).

## ABSTRACTS ON NUTRITION

HINES, C. R.: *Diabetes mellitus: presently recognized concepts of management.* Bull. U. S. Army Med. Dept. IX, 11, 912-919.

An insulin deficiency probably is not the only defect in diabetes, because retinitis and atherosclerosis may occur in well managed cases. Over 95 percent of diabetes can be well controlled. Glycogenesis from body fat and protein is a liver function, but the bodily sources of fat and protein are not inexhaustible. Furthermore, glucose so formed is not usable and cannot be stored, so that ketosis and acidosis eventually result. Death in coma is due to acidosis and dehydration. The author does not favor Tolstoi's free dieting principles. A patient requires 30 to 40 calories per kilogram of body weight per day. The number of grams of protein multiplied by 4 gives the number of calories it supplies, and thus, subtracted from the total calories, leaves the number to be supplied from fat and carbohydrate. The two latter elements usually are employed in the ratio of 2 carbohydrate to 1 fat. To reduce the weight of a diabetic, compute his diet on the basis of his present weight, then withhold enough of the fat to cause his fat stores to be called upon. Fitting the dose of protamine zinc insulin to the patient requires several days of trial and error investigation. Where both regular and PZ insulins are used, the author advises that they be given as separate injections.

MENDENHALL, E. N.: *Tumor of the pineal body with high insulin resistance.* J. Indiana State Med. Ass. 43, 1, 32-36.

Mendenhall attended a family in which 3 of 7 children developed a syndrome characterized by pineal tumor and insulin resistant diabetes. Other constant features of these cases were, marked hirsutism, thick, pigmented skin, pot belly, thickened and hardened nails on the fingers and toes, early dentition (second dentition complete at two or three years), enlarged external genitalia in both male and female and death from infection or acidosis or both. Two of the cases presented also simple cysts of the pituitary gland. All of the 3 cases showed pancreatic fibrosis with hypertrophy of the islands of Langerhans. These cases do not conform to

Pellizzi's syndrome. There is strong suggestion that abnormal pineal function, associated with tumor of the gland, had direct bearing upon the development of insulin resistant diabetes. Mendenhall now is attempting to find some correlation between blood sugar and the pineal body.

BAESJOC, J. F. J.: *Lyophilic desiccation of maternal milk: an initiative of the Netherlands Red Cross.* (International Health Bull., Jan-Mar. 1949, Vol. 1, 7-8).

The author points out that infants fed on maternal milk assimilate vitamins A and C better and have less need of vitamin C than those who receive cow's milk. In the second half of the first year of life, respiratory infection is almost twice as frequent in artificially-fed infants. No ill infant under six weeks ought to be denied maternal milk. The Netherlands Red Cross collects maternal milk chiefly at Amsterdam and processes 30,000 liters per year. The milk is pasteurized, frozen rapidly, and desiccated by a method which causes the water to leave the frozen milk as a vapor. It is dispensed in bottles which produce 100 cc. of maternal milk by adding that much water. Experiments indicate it is equal to mother's milk in all respects.

HODAS, J. H., BRANDON, H. and MALONEY, J. F.: *Treatment of rheumatic diseases with glucuronic acid.* Journal Lancet, 1949, 49, 11, 385-388.

Glucuronic acid is a detoxifying agent, and it enters into the formation of collagen. Patients with various form of arthritis were given doses of glucuronic acid averaging 10 to 15 grains three or four times daily. Early cases of hypertrophic arthritis responded especially well. Sciatica responded very satisfactorily indeed. The authors feel that glucuronic acid works as well in arthritis as any remedy known, and should be carefully tried out by other investigators.

SCOTT, J. M. and GOVAN, A. D. T.: *Anemia of pregnancy in Glasgow and district.* Brit. Med. J. Nov. 12, 1949, 1083-1087.

About 18 percent of all patients at their first visit to an ante-

AMER. JOUR. DIG. DIS.



natal clinic were anemic (i. e., they had hemoglobin values less than 70 percent of normal.) Of those having initially low values for hemoglobin (i. e., slightly less than 70 percent hemoglobin) 29 percent became frankly anemic. Iron was found to be the best form of treatment. Deficient iron storage was regarded as the causal factor. Repeated surveys in other parts of Scotland did not show a high incidence of anemia but a diminished one in patients attending ante-natal clinics. Dietary surveys of some of the Glasgow cases indicated that the diet had been above American standards with respect to iron intake. The authors feel that "social habits and environment" may be more important than iron intake in causing the high incidence of anemia in Glasgow. (If the authors meant alcoholism they did not plainly so state. In any case, no red blood cell counts are recorded or smear examinations mentioned, so that the study was one based exclusively on hemoglobin values.—Abstractor.)

MORGAN, E. H., HALL, R. E. AND CAMPBELL, D. C.: *Hematopoietic activity of parenterally administered beef muscle concentrate in cases of pernicious anemia*. Staff Meet. Mayo Clin. Nov. 23, 1949, 24, 594-597.

A concentrate of beef muscle was administered to 3 patients with pernicious anemia in relapse. Each patient received 20 mg. of the concentrate daily, representing 125 gm. of beef muscle and containing about 1 microgram of vitamin B<sub>12</sub> as determined by microbiological assay. In 2 cases an optimal blood response was obtained and in one case the response was suboptimal. It appears probable, therefore, that the extrinsic factor in beef muscle is identical with vitamin B<sub>12</sub>. It is unlikely that the intrinsic factor of the gastric juice unites with vitamin B<sub>12</sub> to form a third substance responsible for erythrocyte maturation in normal persons. Probably gastric juice normally merely facilitates absorption of vitamin B<sub>12</sub> from the gastrointestinal tract.

TOMPKINS, V. L. AND SCOLAR, F. L.: *Vitamin A, carotene and ascorbic acid content of nursery school lunches*. (Am. J. Dis. Child., Aug. 1948, Vol. 76, No. 2, 184-191).

The total ascorbic acid content of all the noon meals plus the tomato juice exceeded one half of the child's daily requirement. All of the foods served each group on the days studied met the total daily requirements except for 3 days' food served the older group. The preformed vitamin A alone obtained in the nursery school food provided from two to three times the recommended daily allowance, while the carotene supplied an additional amount not included in the preformed vitamin A. It was concluded that the nursery school food analyzed (at the North Texas State College Nursery School) provided vitamin A, carotene and total ascorbic acid in excess of that necessary in one meal, even when that meal is the noon meal of the day.

CODONNIS, A. D.: *Syndrome of diaphragmatic hernia and anemia* (Brit. Med. J., May 7, 1949, 805-807).

Codonnis quotes medical literature to indicate that some 8 percent of cases of esophageal hiatus hernia are associated with anemia. He describes a case of his own which may be unique. A severe anemia persisted for 24 years as did the hernia. At first there was a microcytic anemia and later macrocytic anemia. The final anemia before death from hernial strangulation was hyperchromic macrocytic, but Codonnis does not think it has anything in common with Bierner's (Addison's) pernicious anemia. The causes of anemia in association with diaphragmatic hernia are not clarified.

PLATTNER, H. C.: *Disorders in water and electrolyte metabolism in diabetic coma*. Helv. Med. Acta, 1949, 16, 2, suppl. 23, 71 pp.

This important work illustrated with 40 tables and figures, opens with a review of modern knowledge concerning the composition of body fluids. It is shown that the extracellular and intracellular dehydration of diabetic coma with loss of water and electrolytes, particularly Cl, Na and K, is responsible for the circulatory collapse and partially responsible for the diabetic nephritis. Loss of potassium produces circulatory, respiratory and nervous effects. Hypopotassemia seems to

result from insulin treatment, which mobilizes the potassium and dilutes the blood, since hypopotassemia does not occur during coma untreated, but only 10 to 20 hours after the beginning of insulin therapy. Following adequate doses of insulin, re-hydration is the most important feature in the treatment of diabetic coma. The loss of water and electrolytes mentioned via the urine, through vomiting, hyper-emiation and anorexia, must be corrected by large amounts of fluid. Diabetic coma may call for as much as 5 to 13 liters of water and 21 to 45 gms. NaCl, in all, for complete recovery. On the first day as much as 4 or 5 liters of saline may be needed. Administration of potassium is logical, but should be given only by the mouth, and reserved for those cases who cannot quickly resume their diet or who show symptoms of hypopotassemia.

M. Demole, Geneva.

MARKEES, S.: *A new treatment of diabetic coma*. Helv. Med. Acta, 1949, 16, no. 3/4, 386-389.

The catabolism of dextrose provides the organism with intermediate products which reduce alkali reserve, one of the most important of these being pyruvic acid. Diabetic patients do not destroy pyruvic acid as quickly as normal persons. When an overdose is given to a diabetic the pyruvic acid curve is higher and remains high longer than the dextrose tolerance curve. In diabetic acidosis, the pyruvicemia is 4 to 10 times higher than in healthy individuals and insulin does not correct it. In a search for the regulating agent in pyruvic acid metabolism, Markes first tried vit. B<sub>6</sub>, which acts powerfully against the hyperpyruvicemia of beri-beri, but was found ineffectual in diabetic coma. He concluded that there was difficulty in phosphorylation, and so used coarboxylase, which is the phosphorylated form of vit. B<sub>6</sub> (Ester of acid aneurin-pyrophosphoric). After proving its efficacy in diabetic animals he injected into human beings doses of 100 mg. diluted in 2 to 5 cm<sup>3</sup> of saline fluid, without interruption of insulin (which coarboxylase does not replace) and with addition of vit. B<sub>6</sub>. He does not mention here this new drug, but we happen to know that they agree with the experimental work.

HORLICK, L., KATZ, L. N. AND STAMLER, J.: *The effect of a low fat diet on the spontaneously occurring arteriosclerosis of the chicken*. (Am. Heart Jour., April 15, 1949, Vol. 37, No. 5, 689-700).

Chickens develop atherosclerosis of the elastic and muscular arteries at a fairly early age. At one and one-half years more than 50 percent of chickens show arterial lesions which resemble human atherosclerosis in many respects. A control group of white Leghorn cockerels, 6 to 10 weeks old, were divided into 2 groups. One group was given a diet of chick starter mash and water freely. The other group received a diet containing the same mash from which the cholesterol and fat had been removed by repeated alcohol-ether extractions. The diets were made isocaloric by adding sucrose and vitamins removed in the extraction were replaced. Up to 25 weeks of feeding, none of the chicks on the low fat diet developed gross lesions of the aorta while 3 out of 5 of the controls did. Between 50 and 63 weeks, 3 out of 4 of the low fat chicks and 2 out of 4 of the control group developed aortic lesions. It is seen that lesions thus developed sooner in the control birds than in birds on a low fat diet. After 50 weeks the incidence in both groups became roughly the same. The severity of the lesions was greater in the controls than in the low fat group. Microscopically atherosclerosis was present in both and the structure of the lesions was essentially similar.

Restriction of fat does not prevent spontaneous atherosclerosis in this species but the lesions are less severe when fat is restricted. Exogenous lipid, while not essential to atherosclerosis, accelerates its progress and increases the severity of the gross lesions. Most instances of human arteriosclerosis occur in the presence of normal lipid blood levels. In chickens the blood or tissue lipid levels are not lowered by a fat extracted diet. As an inference from these experiments, it would seem that the evidence at present does not warrant wholesale restriction of lipids in an attempt to prevent the onset of arteriosclerosis. In patients with hypercholesterolemia and those with a bad family history of coronary and cerebral arteriosclerosis, fat restriction may be a judicious measure, but wider application of fat restriction must await more experimental justification.

## EDITORIALS

## THE AMERICAN JOURNAL OF PROCTOLOGY

In March of this year, No. 1 of Vol. 1 of the American Journal of Proctology made its debut. We extend our congratulations to the International Academy of Proctology, official sponsor of this new magazine, upon having created a worthy new member of the galaxy of American medical journals. We especially congratulate Alfred J. Cantor, M.D. of Flushing, N. Y. who as Editor is to be credited with having done a very fine job. The journal follows the usual formula of original contributions, editorials and abstracts, all of which are of highest caliber. It is not difficult to prophesy a good future for the American Journal of Proctology and it is a pleasure to wish it the utmost success.

## THE ACID RESPONSE TO A MEAL

R. A. Jamieson (1) while doing a two-stage surgical operation for the alleviation of complicated duodenal ulcer, found occasion to make an isolated gastric pouch of a large portion of the middle of the stomach with a stoma admitting a catheter through a stab wound. For a period of 2½ months Jamieson studied the acidity and the volume of the pouch secretion. A somewhat remarkable finding was that there was no special secretory response to a meal and only a slight response to the injection of histamine. The other finding which requires notice was that atropine caused a very striking depression of secretion from the pouch.

Jamieson discusses the problem posed by his discovery of an absence of secretory reaction to a meal and asks if it could be possible that the ordinary experience of secretory response, as detected by test meals, could be fallacious. He points out that within the stomach itself, during the early phases of digestion, the pylorus is closed, thus not only preventing escape of acid juice but also the regurgitation of alkaline duodenal fluid. He recalls that Pollard and Bloomfield had often found the fasting secretion more strongly acid than following a test meal. Jamieson's work undoubtedly deserves repetition. As he states, "It seems almost incredible that a secretory response to food by the human stomach, substantiated by so much evidence, can seriously be contested." His work also graphically indicates the value of atropine in the therapy of peptic ulcer.

(1) Jamieson, R. A.: Observations on an isolated gastric pouch in man. *Rev. Gastroenterology*, 17, 1, 49-63.

## THE VALUE OF GASTRIC ANALYSIS

Some authorities are insisting that the analysis of the gastric contents of patients, while still useful in helping to differentiate between a cancer and a benign ulcer of the stomach, is otherwise of such limited value in a clinical examination as to make it unwarranted. The same authorities logically claim also that the adminis-

tration of dilute HCl to persons with achylia gastrica does not serve any very useful purpose. They seem to feel that the entire subject of gastric analysis is an un-fertile field and should be regarded as dead as the dodo. Not only do such authorities not receive the sanction of many seasoned clinicians but the recent work of Fraser (1) in particular has brought the subject suddenly back into the focus of our attention.

It has been long well known that in persons with achylia there occurs a tremendous overgrowth of intestinal bacteria high in the gut, due partly to the elevated pH of the small bowel contents, and perhaps due also to the difference in the chyme resulting from the absence of gastric digestion. Fraser has called our attention now to the possibility that this bacterial overgrowth in the high gut may not be so innocent a phenomenon as we have ordinarily supposed it to be. Most vitamins, but particularly those of the B-complex, represent essential food factors of many bacteria, and Fraser's theory of a contention between the host and the bacteria for available vitamins is not without clinical facts to support it. His illustrations of transient and irregularly recurring specific B-fraction deficiencies in persons suffering from sprue (as well as non-tropical sprue and the celiac syndrome) indicate that these deficiency symptoms and signs can be cured quickly by the parenteral administration of some one of the B-group such as thiamine, nicotinic acid, pyridoxine or riboflavin. Achylia was present in his cases, and he confirmed the high bacterial population in the duodenum and jejunum of these patients. The suggestion is strong that we should be on the lookout for vitamin B-complex deficiency manifestations in persons with achylia. Otherwise expressed, given a case of unexplained recurring or constant B-deficiency syndromes, we should do a test meal to see if achylia is present.

Fraser's hypothesis of bacterial contention for vitamins perhaps may lead eventually to a better understanding of the pathogenesis of Addisonian pernicious anemia. Prior to liver extract, many clinicians felt that the administration of HCl to these cases exerted a slightly ameliorating effect on the cord changes, and sometimes a similar effect was obtained by the use of Acidophilous milk cultures. It should not be forgotten that combined system disease may occur without anemia, and that these cases invariably have shown achylia gastrica. Whatever the relationship of cord changes to vitamin B-complex may be, we are justified in believing that there is a definite relationship inasmuch as B<sub>12</sub> exerts a beneficial influence on them. It is not impossible that other elements in the B-complex also may bear some relationship. Certainly the contention for B<sub>12</sub> itself between the host and the intestinal bacteria is a phase of pathogenesis which has not received sufficient attention. Those rather rare cases of "pure" combined disease without anemia eventually develop an anemia (sometimes only three weeks before death in untreated cases) and it is always a macrocytic hyper-

chronic anemia consonant with the Addisonian blood picture. The point is that these persons go along for months and even years with the characteristic cord changes but without any evidence of a lack of  $B_{12}$ , as judged by their hematological status. These cases are the best argument we know for the dissociation of neural and blood manifestations, and we are aware that the glossitis and stomatitis sometimes respond favorably to the administration of single elements of the B-complex, particularly nicotinic acid and riboflavin.

The author has obtained striking clinical improvements in pernicious anemia patients who, in spite of liver extract or  $B_{12}$  were not doing as well as average, by the intravenous administration of the B-complex group and good results, but less striking ones, by giving dilute HCl by the mouth. Certain other patients with various diseases, but complicated by the presence of achylia gastrica, also have been improved by both these measures. We feel that Fraser may possibly have evolved an idea of real importance, and that the contention for vitamins between bacteria and host is a conception which in itself warrants us in knowing more about the gastric secretions of our patients, no matter what their disease may be.

- (1) Fraser, A. C.: A new mechanism of vitamin deprivation. *B. M. J.*, Oct 1, 1949, 731-733.

#### PINEAL TUMOR ASSOCIATED WITH INSULIN-RESISTANT DIABETES

Edgar N. Mendenhall, M.D. of Fort Wayne, Indiana, during the past 16 years has had under observation three children of the same parents who developed a disease which has apparently not been previously described. The chief features of this obviously rare malady consisted of the presence of a pineal tumor and the eventual development, in all of them, of an insulin-resistant diabetes at the age of seven. These three children all died within a year of the appearance of the insulin-resistant diabetes, either from infection, acidosis or both. In one of the cases it required, according to Men-

denhall's (1) report, 5400 units of insulin to produce a hypoglycemia, while in a second case 1000 units of insulin had little effect on the blood sugar levels. The pinealomas found at post mortem examination measured 2x2x1 cms. or more and presented constant hyperplastic histological features.

Four other children of the same parents were normal. The three which are described in his interesting report presented also certain other abnormal features in addition to the pineal tumors and the insulin-resistant diabetes. All had odd-appearing faces with heavy features; hirsutism; a very rough and thick skin with pigmentation; protruding abdomens; thickened and hardened nails on the fingers and toes; early dentition (first dentition complete at one year and second dentition complete at two or three years), and, finally, enlarged external genitalia in both males and females. At autopsy, all cases presented some degree of pancreatic fibrosis with hypertrophy of the islands of Langerhans. Two of the cases showed simple cysts of the pituitary gland.

In none of the cases were there any symptoms or signs of increased intracranial pressure, such as Pellizzari has described for tumors of the pineal glands.

Physiologists with whom Mendenhall has communicated, including Professor Charles C. Best, do not believe that there is any good evidence that the pineal gland has anything to do with diabetes. Yet the finding of three cases in all of whom a resistant diabetes was associated with definite pineal tumor logically suggests that a great deal of work now should be done on the pineal gland in connection with carbohydrate metabolism. Mendenhall, working in the Fort Wayne Medical Laboratory, is at present interested in discovering some possible correlation between blood sugar levels and the function of this mysterious gland. He states that his results are at least encouraging. It is to be hoped that he will be able to add some increment to our knowledge of carbohydrate metabolism. In the meantime, Mendenhall is to be credited with a very fine, and original series of clinical observations.

- (1) Mendenhall, E. N.: Tumor of the pineal body with high insulin resistance. *J. Indiana State Med. Ass.* 43, 1, 32-34.

## GENERAL ABSTRACTS OF CURRENT LITERATURE

KNUTSON, J. W., SCHOLZ, P. H. AND SCHOLZ, G. C.: *The effect of topically applied fluorides on dental caries experience.* Public Health Reports, 1949, 64, 45, 1403-1410.

The overall reduction in newly carious teeth in fluoride-treated as compared with untreated teeth was 49.3 percent. The reduction in newly carious tooth surfaces, as between the same groups, was 37.9 percent. It was also found that the caries prophylactic effect of topical sodium fluoride was remarkably uniform for the various sections of the mouth in the individual child.

FRANK, R. C. AND LESTER, W. P.: *Congenital reduction of the esophagus.* Radiology, 53, 3, 417-419.

The anomaly of congenital bifurcation of the esophagus is mentioned in several standard text books but the case presented here is only the third reported in the literature and the only

one in a patient beyond infancy. It is also the first in which x-ray studies have been done and the diagnosis established during life. The patient, a 10 year old boy, had begun to experience difficulty swallowing at the age of five. X-ray examination revealed a bifurcation of the mid-esophagus for a distance of 13 cms. The swallowed food went both ways, reunited above the cardia, and entered the stomach normally. Surgery is contemplated at a later date.

UNGLEY, C. C.: *Vitamin  $B_{12}$  in pernicious anemia: parenteral administration.* Brit. Med. J. Dec. 17, 1949, 1370-1377.

Ungley used the pure crystalline vitamin  $B_{12}$  isolated by Lester Smith, on 53 cases of pernicious anemia in relapse. Individuals varied widely in their response to a single dose, although a single dose of 10 micrograms or more usually produced remissions. The most valuable guide to hematological

improvement was the rate of increase of red blood cells. Individual requirements vary with such factors as age, sex, body weight, fever and metabolic rate. The rate of excretion of vitamin  $B_{12}$  in the urine probably is an important factor. Generally, there is less variation in response to treatment when larger doses are used. Twenty-one patients with neurological manifestations have been followed by Ungley for 6 to 15 months and these manifestations improved or remained unchanged, and fresh symptoms have not appeared. In uncomplicated cases, he found that usually a standard dose of 30 micrograms every three weeks sufficed for maintenance purposes, although wide individual requirements were noted.

Patients with subacute combined degeneration should receive at least 40 micrograms weekly for the first 6 months, and 20 micrograms weekly thereafter, although some will need more. The dose would be doubled or even trebled on the slightest appearance of sore tongue, fall in red blood cell count, or neural symptoms. (In patients with hypothyroidism who are using thyroid extract, the basal metabolism needs frequent checking, as cumulative effects of thyroid may induce tachycardia and diuresis with loss of Vitamin  $B_{12}$  in the urine.—Abstractor).

SMITH, E. LESTER: Crystalline anti pernicious anemia factor. *Brit. Med. J.* Dec. 17, 1949, 1367-1369.

The author provides a valuable review of the procedures employed in the final isolation of vitamin  $B_{12}$ , with accessory references to the techniques employed. Chiefly he shows that the tardiness with which the active principle of liver extract was isolated (more than 20 years after the Cohn fraction), was in large part due to the absence of a simple method of testing new fractions, so that each had to be laboriously tested out on patients with pernicious anemia in relapse. Much of Smith's analytical work depended upon partition chromatography, and he found that nearly all the clinical activity was concentrated in the pink fraction. His final triumph in seeing the pure substance crystallize out of aqueous acetone was forestalled by the announcement that the Merck team under Karl Folkers in New Jersey had anticipated him.

Now, microbiological assay permits standardization actually in gravimetric terms of the new vitamin. The only substances known to be physiologically active in smaller doses are such poisons as radioactive plutonium and botulinus toxin. It is true that vitamin  $B_{12}$  which has been isolated in crystalline form does possess clinical activity in pernicious anemia but its importance as compared with vitamin  $B_{12}$  is not determined. Cobalt is represented by an atom in the molecule of  $B_{12}$  and this fact has caused speculation as to the possible importance of this trace element in nutrition. The isolation of  $B_{12}$  from the cultures of *streptomyces griseus* had greatly simplified commercial production of  $B_{12}$ .

LA TONA, S. R. AND LE FEVRE, P.: Relationship of dicumarol absorption to gastric free hydrochloric acid. *Amer. Heart J.*, 1949, 38, 5, 743-746.

The extreme variability of the prothrombin time response to similar doses of Dicumarol has long been recognized, and it led to the question of a possible relationship between Dicumarol absorption and gastric acidity. But a clinical experiment designed to elucidate this problem failed to show any relationship between the prothrombin response to Dicumarol and the amount of free HCl in the gastric contents. In patients with achylia there was less variability in the prothrombin time response than in those patients who possessed free acid. The significance of this latter finding is not at present clear.

FORD, W. J.: Unrecognized pernicious anemia in patients with chronic arthritic complaints. *Illinois Med. J.* 1949, 96, 5, 318-321.

Ford describes two cases of pernicious anemia with cord changes which, before being referred to him, had mistakenly been treated for "arthritis" of the lower extremities. These cases afford valuable illustrations of the fact that, unless pernicious anemia and its cord manifestations are constantly kept in mind, the diagnosis frequently will be missed, and thus irreparable nervous tissue damage may be permitted to develop with tragic results to locomotion and the happiness of

the patient. The author stresses also the mental changes sometimes associated with Addisonian anemia and shows that these may easily be confused with cerebral arteriosclerosis in elderly persons. (In younger persons, mental changes seem to result from the anemia *per se* and disappear as a rule as the blood count returns to normal.—Abstractor).

REYNOLDS, R. P. AND CANTER, M. O.: Hidden gastroduodenal lesions. *Gastroent.*, 1949, 13, 4, 280-284.

This article tells why not a few serious organic lesions of the stomach and duodenum are not diagnosed prior to operation, and why some of them are not diagnosed even at operation. The report of a non-functioning gall bladder often directs all the attention to the biliary tract but we should remember that a duodenal ulcer may cause a gall bladder to fill poorly or not at all. A negative x ray report should never be considered final, in cases in which the history and the clinical examination suggest organic lesions. Even at operation if the stomach is not opened, posterior wall ulcers can be missed.

SCHLOSS, E. M.: Thephorin (phenindamine) in the treatment of gastrointestinal allergy. *Gastroent.* 1949, 13, 4, 311-318.

Thephorin was found to bring about a high degree of relief from the symptoms of gastrointestinal allergy. The drug is an antihistaminic with anticholinergic effects. The diagnosis of G. I. allergy was sometimes made by intubation studies of the jejunum, by elimination diets, and by observing the effects of suspected allergens on the rectal mucosa.

MASON, J. AND SCHWARTZ, S. O.: The co-existence of pernicious anemia and chronic lymphatic leukemia. (*Illinois Med. J.*, 96, 3, 197-198).

A case is presented which seems to be one of pernicious anemia complicated by chronic (leukemic) lymphatic leukemia. The occurrence of the two diseases may represent a simple coincidence. Since the life expectancy in Addisonian anemia has been improved, such coincidence might be expected to increase. Four previously reported cases can be considered acceptable, of which two were also chronic lymphatic in type.

MCNEELY, G. R.: Parotid gland neoplasms. (*Miss. Valley M. J.*, Sept. 1949, 71, 5, 161-164).

The author emphasizes the fact that we seldom know, from clinical examination, what kind of tumor the parotid may contain, and even the pathologist may have difficulty classifying them after removal. He presents 3 cases, with the following microscopic diagnosis,—mixed tumor, embryonal cell carcinoma, and mixed tumor with basal cell carcinoma. Every unilateral swelling of the parotid gland should be investigated with neoplasm in mind. X-ray therapy should be used after surgery, and not before surgery. Such radiation treatment improves the cosmetic end results.

GARLAND, E. A.: Spontaneous retroperitoneal hemorrhage simulating appendiceal abscess. (*J. Indiana St. Med. Assoc.*, Sept. 1949, 42, 9, 897-902).

A case is fully described of a 2 year old female child whose symptoms and signs, including abdominal mass, temperature, white blood count, suggested an appendiceal abscess, but emergency laparotomy revealed a large fluctuant retroperitoneal mass. Evacuation obtained 500 c. c. of fresh blood and clots. The origin of the hemorrhage was not determined. A good recovery resulted. Primary clinical examination did show, however, definite anemia and an absence of abdominal rigidity.

SILVERMAN, F. N. AND CAFFEY, J.: Congenital obstructions of the alimentary tract in infants and children; errors of rotation of the midgut. *Radiology*, Dec. 1949, 53, 6, 781-788.

Ectopia of the cecum, best demonstrated by barium enema, is the distinctive finding in cases of malrotation of the embryonic midgut, a condition which commonly causes mild obstructive symptoms.

HEPKE, H. W.: *Reliability of roentgen examination in hypertrophic pyloric stenosis in infants.* Radiology, Dec. 1949, 53, 6, 789-792.

In 205 cases in whom x-ray diagnosis of hypertrophic pyloric stenosis had been made, laparotomy showed the diagnosis to be correct in 99 per cent. In only one of 150 cases clinically so diagnosed but normal roentgenologically, was a tumor found at surgery. The most reliable means of diagnosis of pyloric stenosis are the pyloric opening time and the pyloric string sign. The x-ray method of diagnosis should be used in all early and doubtful cases because of its reliability.

ORR, J. M. AND JOHNSON, H. D.: *Vagotomy for peptic ulcer.* Brit. Med. J. Dec. 10, 1949, 1316-1319.

Vagus resection is a powerful weapon against ulcer recurrence and produces an apparently permanent reduction in the degree of gastric acidity. In cases with pyloric stenosis or chronic penetration of the ulcer, or of history of hemorrhage, vagotomy should be combined with either gastroenterostomy or gastric resection. The patient most suitable for vagotomy is one in whom there is a clear association between worry and relapse. The authors do not employ vagotomy for gastric ulcer. They prefer hemigastrectomy to subtotal gastrectomy because of the lesser shock and risk and the post-operative absence of the "small stomach syndrome." Vagotomy has had the unexpected effect of relieving constipation. Postoperative gaseous distention is the most troublesome complication. Yet 25 per cent of patients continue to complain of ulcer symptoms or suffer from recurrences after initial periods of well-being. Their results suggested that vagotomy plus gastroenterostomy may prove to be an adequate procedure with a minimal risk of stomal ulcer.

COPE, V. Z.: *Visceral actinomycosis.* Brit. Med. J., Dec. 10, 1949, 1311-1316.

The only possible means of infection by actinomycosis is from one human being to another, and the commonest habitat of the organism is within the crevices of carious teeth. The organism may be swallowed with the saliva and subsequently gain access to the wall of gastrointestinal tract via ulcerated areas. It frequently forms granulomata which may be easily mistaken for cancer. When the granuloma softens and forms pus, this has a tendency to seek the surface of the body. The organism may reach the peritoneum as a result of the perforation of a viscus, and may at times produce a subphrenic abscess. The vermiform appendix is a favorite habitat of the organism and consequently perforative appendicitis is the commonest precursor to abdominal actinomycosis. Actinomycosis is the "most misdiagnosed disease." Yet today, it is more common than syphilitic gumma. In the treatment of actinomycosis, sulfonamides, particularly in association with massive and long-continued doses of penicillin are best. Streptomycin and bacitracin also are of value. When iodine is to be given, the best method is 5 minims of tincture of iodine in a glass of milk.

BURNARD, E. D.: *Hirschsprung's disease in infancy.* (Brit. Med. J., Jan. 21, 1950, 151-156).

In cases in which Hirschsprung's disease is present at, or soon after birth, it is characteristic to find constipation yielding temporarily to enemas, but soon returning. Vomiting is the earliest symptom. The diagnosis must rest on x-ray examination. Pathological examination indicates that below the dilated and hypertrophied bowel, the gut possesses no ganglion cells in the myenteric plexus. True Hirschsprung's disease must be differentiated from "dyschezia", a term used by Hurst to indicate a state of chronic constipation dependent on faulty habits, but curable by proper attention. The two-stage rectosigmoidectomy with restoration of bowel continuity, devised by Swenson and Bill in 1948, gives good results in older patients who survive with the disease; but, in the very young infant, it ought not to be done until sufficient time has elapsed to permit an opinion as to the severity of the case. There are some cases in which the affected segment is too long to permit excision and approximation of the upper portion to the anus.

JUNE, 1950

WALTMAN, W. AND FAHEY, M. M.: *Vagotomy—immediate results in 28 cases and later results in 68 cases.* (Proc. Staff Meet. Mayo Clin., 24, 20, 501-506).

Follow-up data were available on 68 of 77 cases on whom vagotomy was performed prior to Jan. 1, 1948, an average of 18 months before this study. Of 42 cases re-examined, 76.2 percent had complete relief of ulcer pain. Although 80.9 percent had lost gastric tone and motility 2½ weeks after operation, ten months after operation 70.3 percent and 18 months after operation 79.4 percent had regained normal tone. Of the entire group of 68 cases, results were excellent in 70.5 percent, unsatisfactory in 13.2 percent and poor in 16.1 percent. Vagotomy alone was done for D. U. In 16 of these 68 cases and in this group excellent results were obtained in 56.2 percent, unsatisfactory to poor results in the balance.

MARSHALL, S. F. AND WILKINSON, S. A.: *Present situation in the surgical treatment of peptic ulcer.* (Texas St. J. Med., 45, 10, 697-701).

Surgical intervention is necessary in 10 percent of duodenal ulcers and 30 percent of gastric ulcers. Partial gastrectomy is the best method of treating complicated ulcer. Vagotomy does not heal a high percentage of duodenal ulcers, but is of value in treating recurrent ulcer, also in cases of massive hemorrhage necessitating surgery.

MCKIERFEL, B. B.: *Some aspects of vitamin B<sub>12</sub> complex and its deficiencies.* J. Indian Med. Ass. XIX, 2, 42-46.

By "vitamin B<sub>12</sub> complex" the author apparently means vitamin B<sub>12</sub> complex minus thiamine. He emphasizes the point previously made by others, that large doses of a single purified vitamin may upset the enzyme systems of the body. The equilibrium may then be restored by the use of liver extract (especially crude liver extract) since it contains the various B enzyme systems in well-balanced proportions. He thinks that liver extract and brewer's yeast are so effective not because they contain a large quantity of vitamins but because they contain them in balanced proportions. He also advises that in cases in which defective absorption or storage are suspected that vitamins ought to be administered parenterally.

DWIVEDI, J. K.: *Anal fissure: its treatment.* J. Indian Med. Ass. XIX, 2, 39-40.

The author uses palliative treatment in acute superficial fissures and claims 100 per cent cures within 2 weeks. Palliative treatment includes the use of petrolatum, local 1 per cent cocaine ointment, and the injection of a long-lasting local anesthetic into the external sphincter and muscle to relieve spasm, also the local application of new carbolic acid or ichthyol. When the fissure shows signs of chronicity (induration of margins, presence of a sentinel tag, a submucous abscess or a dorsal fistula) operative treatment is employed.

ROBBIN, L. AND ERDMAN, G. L.: *Cystic fibrosis of the pancreas.* Arch. Pediat., 67, 1, 8-18.

A case of cystic fibrosis of the pancreas is described in which there was an absence of squamous metaplasia of the lining epithelium of otherwise characteristically affected bronchi. This may have been due to the heroic doses of penicillin used, as well as the administration of large amounts of vitamin A. The authors feel that the squamous metaplasia usually found in the bronchial epithelium in cases of cystic fibrosis of the pancreas is due, not to the same process as occurs in the pancreas but to a secondary deprivation of vitamin A from faulty absorption resulting from the pancreatic disease. This case presented anasarca and ascites which did not depend on renal disease and did not respond to the administration of salt poor human albumin. The edema was obviously due to a disturbance in sodium metabolism, and it was got rid of by the use of a mercurial diuretic.

WALTON, SIR JAMES: *Progress of gastric surgery in the last half century.* Brit. Med. J. Jan. 28, 1950, 266-270.

The author traces various changes in gastric surgery and

gives a permanent place to gastroenterostomy in certain types of ulcer. Marginal ulcers always need operation and a gastrectomy should be done. The author feels that should he personally develop a perforated peptic ulcer he would prefer surgery, inspite of the good results obtained by Bermon Taylor without operation. He finds the frequency of marginal ulcer increasing in England. He feels that the great improvement in mortality in gastric surgery has been due to progress in operative technique, and "that the great skill of this technique has reached its zenith." He believes that medical cures of ulcer and cancer will result from unfettered research in an unregimented profession, eventually rendering gastric operations mere curiosities of the past.

JONES, F. A., PARSONS, P. J. AND WHITE, B.: *Acute perforated peptic ulcer*. Brit. Med. J. Jan. 28, 1950, 211-215.

The authors analyze 490 cases of acute perforation of peptic ulcers treated from 1938 to 1948. During the first 3 years the operative mortality was 27 percent. During the last two years it was only 4 per cent. It was thought that the improvement was mainly due to better anesthesia and the routine use of antibiotics. They give 200,000 units penicillin pre-operatively and 100,000 units every 6 hours intramuscularly for 3 days, while sulfonamides are used orally for 3 days as well. They do not emphasize gastric suction but use a Ryle tube in the stomach for the first 24 hours, or longer if there should be any accumulation of gastric contents.



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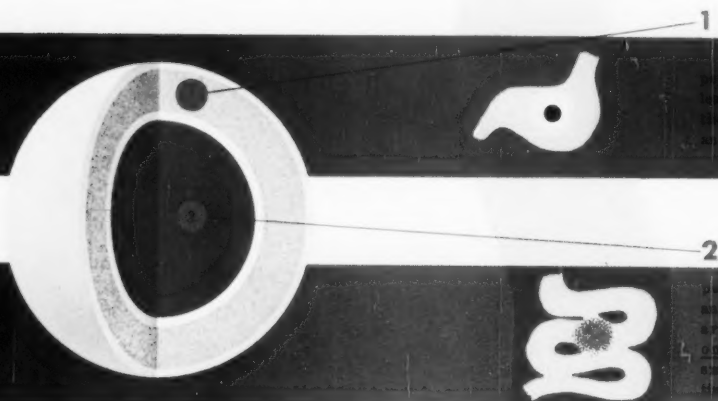
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**references**

1. McGavack, T. H., and Klotz, S. D. Bull. Flower Fifth Ave. Hosp., 9: 61, 1946. 2. Weissberg J., et al.: Am. J. Digest Dis., 15:332, 1948.



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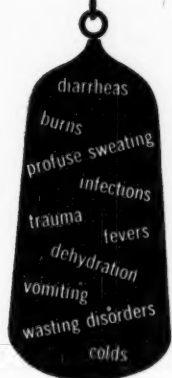
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## *Ionic balance in acidosis...*



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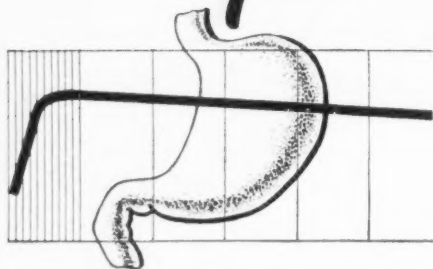
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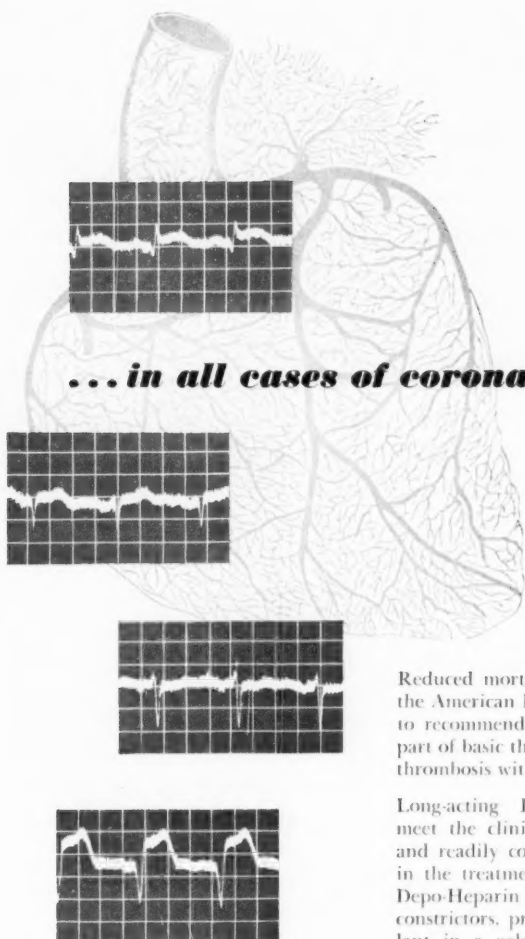
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1. Wright, et al: *Am. Heart J.*, 36, 801 (Dec.) 1948.

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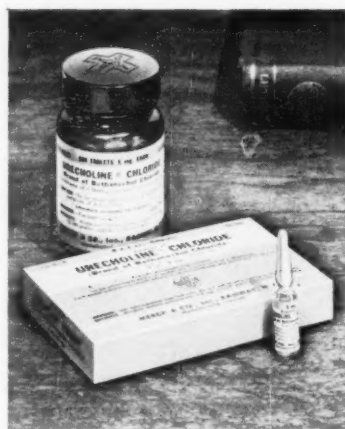
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\*Orent-Keiles, E., and Hallman, L. F.: The Breakfast Meal in Relation to Blood-Sugar Values, Circular No. 827, United States Department of Agriculture, Bureau of Human Nutrition and Home Economics, Agricultural Research Administration, Dec., 1949.

The Seal of Acceptance denotes that the nutritional statements made in this advertisement are acceptable to the Council on Foods and Nutrition of the American Medical Association.



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1. Weiss, S., et al.: *Rev. Gastroenterology* 16:501-509 (June) 1949.

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## NEW PHS UNIT

Formation of a new unit under the Public Health Service, Federal Security Agency, to develop a radiological health program to meet potential health hazards created by increased use of radioactive materials and radiation-producing machinery was recently announced.

Established within the recently formed Engineering Resources Division of the Public Health Service, the new unit is known as the Radiological Health Branch and is under the direction of Dr. Edwin G. Williams, a Public Health Service medical director.

The Radiological Health Branch will correlate radiological health activities in the Public Health Service, develop a training program in radiological health for Service officers and other public health workers, and act as a source of information on radiological health for other units of the Service, for other Federal agencies, and for State and local health agencies.

Surgeon General Leonard A. Scheele of the Public Health Service said the new branch was established "because of the recent rapid increase in the use of radioactive materials and radiation-producing machines in hospitals, industry, experimental laboratories and other places throughout the country."

"This in turn," Dr. Scheele said, "has created a need for some consideration in the Nation's public health program of the control of potential radiation hazards."

Dr. Scheele said that radioactive materials in use include radium and radioactive isotopes, such as radioiodine, radio-iron, radio-phosphorus and radio-sodium. Radiation-producing machines, he said, include X-rays, fluoroscopes, cyclotrons, betatrons, and other atomic-particle accelerators.

#### FRANK F. LAW, VICE PRESIDENT OF WYETH INCORPORATED, DIES AT 56

Frank F. Law, Vice President of Wyeth Incorporated, died at the age of 56, on the morning of June 5, at the University of Pennsylvania Hospital, Philadelphia, after an illness of several months duration

following nearly forty years of service to the profession of pharmacy.

Mr. Law was born in Edwinstown, near Wilkes-Barre, Pennsylvania, in 1894. After graduation from high school, he worked for two years at White's Drug Store in Camden, New Jersey, and attended Temple University College of Pharmacy. Following his graduation from Temple in 1917, he enlisted in the United States Navy during the first World War and shortly afterward went overseas with the Philadelphia Methodist Hospital unit headed by Dr. Robert Le Conte, noted physician. Though he was trained and enlisted as a pharmacist, the Navy switched Law to personnel and detail work. In this capacity he served for twenty-two months at the Navy's largest hospital, the 1000-bed Base Hospital No. 5 at Brest, France.

Before the war, Law's ambition had been to own a retail drug store but his horizons had widened and, on his return home, he determined to get into the manufacturing end of the business. He was hired by the late Stuart Wyeth, then president of the old John Wyeth & Brother company, who saw possibilities in the young Navy veteran and almost immediately began grooming him for an executive position. Law was put to work in every department, one after another, the fluid extract, tincture, elixir, granular effervescent salts, pills, tablets and soluble capsules, first as a floor hand, then as supervisor and finally production manager of the entire company, which then had eight branches. When American Home Products Corporation acquired Wyeth, Law became vice president and general manager, and president in 1934.

In 1943, American Home Products merged five companies into an ethical drug division, using Wyeth as the nucleus and with Harry S. Howard, then head of A. H. P., as president. The new firm was called Wyeth Incorporated, and Law became vice president in charge of industrial relations as well as pharmaceuticals and penicillin manufacture, and president of John Wyeth & Brother, Inc., of Canada.

Temple University honored Mr. Law in September, 1948, by awarding him the honorary degree of Doctor of Science.

During Mr. Law's long years of association with the pharmaceutical profession, he held many offices in important pharmaceutical groups, and at one time served as president of the Philadelphia Drug Exchange, the oldest drug trade body in the United States. He was a member of the executive committee of the American Drug Manufacturers Association, and was also a member of the American Pharmaceutical Association. Mr. Law was deeply interested in the alumni affairs of Temple University and was president of the General Alumni Association from 1942 through 1944. He was also a trustee of the University.

Mr. Law resided at 320 Brownling Road, West Collingswood, New Jersey, and was a resident of that town for at least twenty-five years. In addition to his active business life, he had several hobbies, among which gardening and golf were his favorites.

Surviving Mr. Law are his wife, Marie Hurley-Law, and his four children, Thomas, Frank, Mary Louise, and John.

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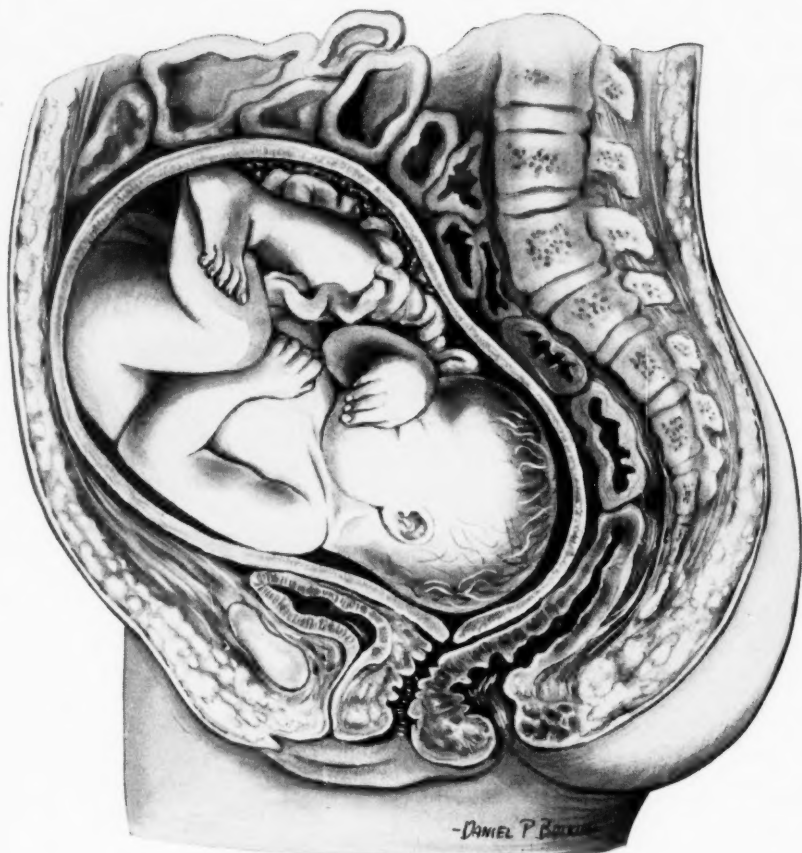
Relief is quick... Kaomagma with Pectin  
soothes and protects inflamed intestinal  
mucosa. Cramps and distention are  
promptly relieved.

**Consolidates stools . . . checks fluid loss  
. . . restores patient's comfort.**

*Bottles of 12 fl. oz.*



WYETH Incorporated, Philadelphia 3, Pa.



**Constipation in pregnancy**, which is the general rule, may be managed without harshness or irritation—through the gentle, easy stimulation of peristalsis produced by Metamucil.

Providing soft, plastic, water-retaining bulk, Metamucil encourages normal elimination without undue pressure, does not interfere with digestion or vitamin absorption and is bland in taste.

**METAMUCIL®** is the highly refined mucilloid of a seed of the psyllium group, *Plantago ovata* (50%), combined with dextrose (50%).



RESEARCH IN THE SERVICE OF MEDICINE **SEARLE**